THE PRINCIPLES

OF

CLINICAL PATHOLOGY

A Text-Book for Students and Physicians

BY

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AUTHORIZED TRANSLATION FROM THE THIRD GERMAN EDITION

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TRANSLATOR'S PREFACE

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THIS volume is translated from the third German edition of Professor Krehl's " Pathologische Physiologie." I have, however, used the title of the first German edition,—viz., " The Principles of Clinical Pathology." This change was made partly because the terms pathological physiology are comparatively unfamiliar to the English and American profession, and partly because it seemed desirable to emphasize the fact that the book deals especially with the problems that confront the clinician.

A literal translation was not attempted. Many abstract discussions have been abbreviated, and in a few places the material has been slightly rearranged, in order to present it in what seemed to be a more natural sequence. Yet no alterations of the author's views have been made, except these were indicated by enclosing them in parentheses; and I have endeavored throughout to maintain the spirit of the original work. A few paragraphs have been added, mainly upon subjects that have attained a certain prominence in the recent American literature, such as the subjects of blood-pressure, surgical shock, and hemorrhagic pancreatitis.

The original edition contains copious references to the German literature. Many of these have been omitted, more especially those referring to the older literature and to the well-known German text-books. In their place, I have added quite a number of English references, which may be of some assistance to those who do not read German and who desire to look up more elaborate discussions of many of the subjects.

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Unfortunately our own literature is often rather fragmentary; for many of the fields dealt with have been developed almost exclusively by continental writers.

In conclusion, I desire to express my indebtedness to Drs. W. E. Garrey, George Blumer, and W. F. Beerman for assistance in reading and correcting portions of the manuscript.

A. W. HEWLETT.

SAN FRANCISCO.

PREFACE TO THE THIRD EDITION

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In the present edition, a large part of which has been re-written, the attempt has been made to include the results of work published since 1897. Yet, in spite of the great pains taken, I dare not assert that all has been included and that even important researches have not been left out. I do not beg indulgence for such omissions, but can only state that I have never intentionally neglected to mention an important research, and that I have endeavored to make the book as complete as possible. Whoever has attempted to follow the literature in so many fields will recognize how difficult it is to master even fairly well the great diversity of material.

L. KREHL.

TUBINGEN, August, 1904.

FROM THE PREFACE TO THE SECOND EDITION

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THE desire to write a book of this character arose from the conviction that two things are essential for a thorough knowledge of internal medicine. The first of these is skill in the art and technic of clinical medicine, which is only to be acquired by long and careful practice at the bedside. The second is the ability to judge disease in accordance with biological principles, for the study of disease is, ideally at least, an exact natural science.

It is unnecessary to discuss the question as to which of the two is the more important. Both are necessary, and a deficient knowledge of either is detrimental to the clinician. If the latter be neglected, he becomes a mere routinist; whereas if insufficient attention be paid to the former, he becomes an impractical theorist.

The whole tendency of modern times precludes the possibility that the practical side of medicine should be neglected, for the extreme value of medical art and technic is now universally recognized. Unfortunately, however, this recognition has led to a certain antagonism toward theoretical and scientific work. Yet we must remember that, now as always, the solid foundation of all clinical knowledge rests upon the sciences of anatomy, physiology, and pathology; that, without these, technical skill in medicine would avail but little; and that the activities and views of the medical profession sink

proportionately to their remoteness from the firm scientific foundations, and proportionately to the degree to which the clinician ceases to be a natural scientist. The purpose of this book, therefore, is to contribute to our knowledge of, and to awaken interest in, the theory of disease processes.

L. KREHL.

LEIPZIG, March, 1898.

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INTRODUCTORY NOTE

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KNOWING its worth, I very gladly agreed to write a brief introductory preface to an American edition of Professor Krehl's well-known work. Not that it needs any words of commendation. A successful book in Germany, it has already been translated into several languages, and has long since passed beyond the probation stage; but a few words from me may serve to introduce it to the English-speaking profession. Those of us who were brought up on Williams's "Principles of Medicine" recall the pleasure and the profit derived from it, mingled now with the regret that we have no work of the same character to place in the hands of our senior students. This want Professor Krehl's book will supply. Herter's "Lectures on Chemical Pathology" cover part of the ground, and Cohnheim's well-known "Lectures on General Pathology" is somewhat similar. In Professor Krehl's work disease is studied as a perversion of physiological function, and the title "Clinical Pathology" expresses well the attempt which is made in it to fill the gap between empirical and scientific medicine. The facts presented are derived in part from studies upon patients, and in part from experiments upon animals, designed to explain clinical problems. The author has had the advantage of prolonged laboratory training, to which has been added that accurate knowledge of disease to be had only by years of study and teaching in the wards. For such a work as this there is at the present time great need. Every few years the laboratories seem to run ahead of the clinics, and it takes time before the facts of the one are fully appreciated by the other. In the complexity of the problems, sometimes in the fascination of the scientific side, we are apt to lose sight of the practical application

to diagnosis and to treatment of the facts obtained in the laboratories. The surgeons have invaded the medical wards with great advantage to our patients, and in many diseases to the great improvement in the art of diagnosis. How helpful it would be if clinicians had always at hand skilled physiologists, pathologists, and chemists to apply their most advanced technique to clinical problems, and not the technique alone, but the biological and chemical principles upon which medicine as an exact natural science is founded. Principles, as Plato reminds us, require constant revision and consideration; and this book, representing a revision to date of the " Principles of Clinical Pathology," will be most helpful to all students and teachers who wish to know the scientific basis of our art.

WILLIAM OSLER.
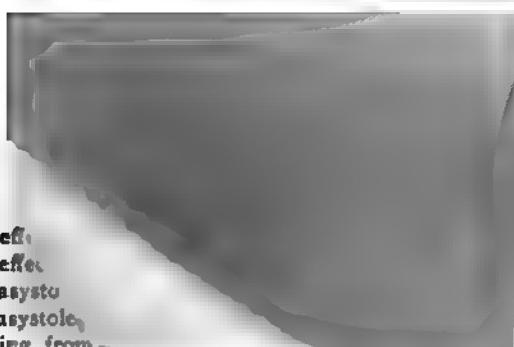
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INTRODUCTION

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PATHOLOGICAL physiology is one among the sciences that
contribute toward our knowledge of diseased processes. In his
famous book on "General Pathology," Cohnheim has defined
disease as a peculiar, abnormal course of the same processes
that make up the life phenomena of healthy individuals. We
term these vital processes normal when they occur in the ma-
jority of individuals and when these latter feel well and are
able to accomplish their average amount of work.

In many instances, it is easy to determine whether the
functions of the body are following a normal or an abnormal
course; in others, the question is a very difficult one to decide.

The whole series of living beings, from the lowest up to the
highest, are liable to be afflicted with disease. Yet different
species, even though they are closely related, may vary con-
siderably from one another, not only in their morphological but
in their functional characteristics. For example, it would be
pathological if a mammal excreted as much uric acid in its
urine as does a normal bird. The question as to whether a
given function is or is not normal can only be answered by
comparing individuals of the same species.

These remarks might appear superfluous, inasmuch as the
primary object of this book is to discuss pathological disturb-
ances in man. Yet a satisfactory understanding of these latter
is not possible except we make critical use of the data obtained
from animals.

I shall not attempt to discuss the outlook that the method
of comparative study opens for us in our knowledge of patho-
logical proce   itherto this method of study has played
it a minor   evelop this field, for the means and

opportunities for pursuing this line of work have been lacking. Yet if pathology is to remain abreast of the other branches of biology, we must have a closer relationship between the pathological and the veterinarian laboratories, and the natural diseases of animals must be studied with a view to the light that they may throw on those of man. Even now, extensive use is made of animal experiments in the study of pathological processes and these experiments have become an almost indispensable aid in such study. In estimating the value of these experiments, however, due regard must be paid to the morphological and functional differences between man and the animals used.

Very considerable individual differences may occur even within a single species. For example, there are men whose stomach contents at the height of digestion contain no free hydrochloric acid, and, although such men differ in this respect from the great majority of their fellows, nevertheless they may show absolutely no digestive symptoms and no diminution in their capacity for work. In my opinion, such individuals can hardly be regarded as being sick, although it must be acknowledged that they stand near the border line between the normal and the pathological. Another class of men show for years clear and unmistakable functional disturbances in some organ or group of organs, and yet they are not incapacitated to the slightest degree for work. Theoretically such men are sick; practically, we hardly know whether to say they are sick or healthy.

The physician must be clear in his own mind about this great difference between the theoretical and the practical; and although we are dealing in this book principally with the former, yet it will not be amiss to emphasize this fact, that many individuals who show definite pathological changes are perfectly healthy to all practical intents and purposes.

We should designate as diseased, therefore, all those life processes which differ from the ones that occur in the majority

of the members of a species, and which, in addition, affect the individual's capacity for work or the duration of his life.

All theories of life processes, physiological as well as pathological, must be carried back to the elementary constituents of the body. Disease arises from changes in a certain set of cells, or of organs, or of groups of organs; for the cells that normally work together are not necessarily grouped together, but they may be distributed over different parts of the body. We are learning more and more that certain functions necessitate the combined action of different classes of cells.

Functional disturbances naturally coincide with, and are caused by, physical, chemical, or morphological changes in the body cells. This dictum is in no way altered by the fact that these chemical and morphological changes may not be demonstrable with the methods at our disposal. It is customary to distinguish those disturbances in which no such changes in the cells have been found (functional disturbances) from those in which such changes have been demonstrated (organic lesions). Yet this distinction is a more or less accidental one, depending as it does upon what happens to be the state of our knowledge at the time when the division is made.

A complete theory of pathological phenomena must embrace not only a knowledge of the functional disturbances in the affected cells, but a knowledge of their chemical, physical, and morphological changes as well. At present, our knowledge in all these directions is satisfactory for only a few diseases. For others, it has developed along functional and anatomical lines, for a third group, along functional and chemical lines, and finally, for a fourth group, the functional changes alone are known to us and we are ignorant as to their anatomical or chemical basis.

The development of our knowledge in one or another of these directions depends in the first place upon the degree to which our methods of investigation can solve the problems pre-

sented. These methods will suffice for certain problems in certain diseases but not for others, so that we have an unequal development along different lines. In the second place, the master minds of the time tend to develop our knowledge along the lines that happen to interest them most, and these lines gain thereby a certain prominence. Controversies have been waged and still are waged as to which is of greatest importance, the functional, chemical, or morphological view of disease. The uselessness of such a controversy is apparent when we remember that all these changes necessarily go together and that we must look at a disease from every point of view. Nevertheless, it is true that one point of view may be more luminous than another in respect to any particular class of diseases.

Diseases result either from primary defects in the living protoplasm or from the protoplasm being placed under such abnormal conditions that it cannot compensate for the changes in its environment. In the first class of cases, the abnormality consists in an improper organization of the protoplasm. The affected individual is then either diseased from birth, or he is born apparently healthy but is unable to withstand the ordinary wear and tear of life as a normal person should. Consequently, the structure, composition, or functions of his tissues suffer. Such primary endogenous weakness apparently plays a not inconsiderable rôle in the etiology of disease.

Of greater importance, however, is the effect that injurious external influences exert upon the living substance of the body. When these injuries affect the composition, structure, or functions of the cells, they become causes of disease. These causes are of the most varied kinds. Heat and cold, humidity and dryness, electricity, chemicals, all these may affect the body; but more important than any of them is the penetration of abnormal forms of life into the body.

Whether a man shall become sick or not, depends, therefore, in the first place, upon the way that he is originally constituted

(endogenous causes), and, in the second place, upon the more or less accidental injuries to which he is exposed (exogenous causes). Furthermore, the effectiveness of the latter class of causes depends largely upon factors that lie within the individual. There are, indeed, poisons, which, in a certain dose, will kill practically any one, and there are infections that will attack all or nearly all individuals exposed to them. Nevertheless, the majority of all infectious and toxic processes affect only a certain proportion of the individuals exposed. The causes of this difference in susceptibility are naturally complex and not always the same; but in the main they depend upon the physiological organization of the individual.

In a complete discussion of diseased phenomena, the vital processes and the alterations in these processes and in the elementary constituents of the body must be considered from various points of view. In the present book, we propose to present only one of these. Just as physiology deals with the functions of the normal body, so pathological physiology deals with the functions when organs are placed under pathological conditions; and this is the subject of our discourse.

The field covered by this book serves, in the main, to fill out the gap left in the subject of pathology after the subjects of general pathology and of special pathological anatomy have been eliminated. In classifying the material, I have followed the classification that is customary in the German universities, and I have utilized material that has especially appealed to me as a clinician. Many subjects that are usually discussed in our text books on general pathology, such as local circulatory disturbances, have been omitted, even though they should rightly be included in a book of this character. Whether the choice of material has been a fortunate one or not, remains to be decided.

THE PRINCIPLES

OF
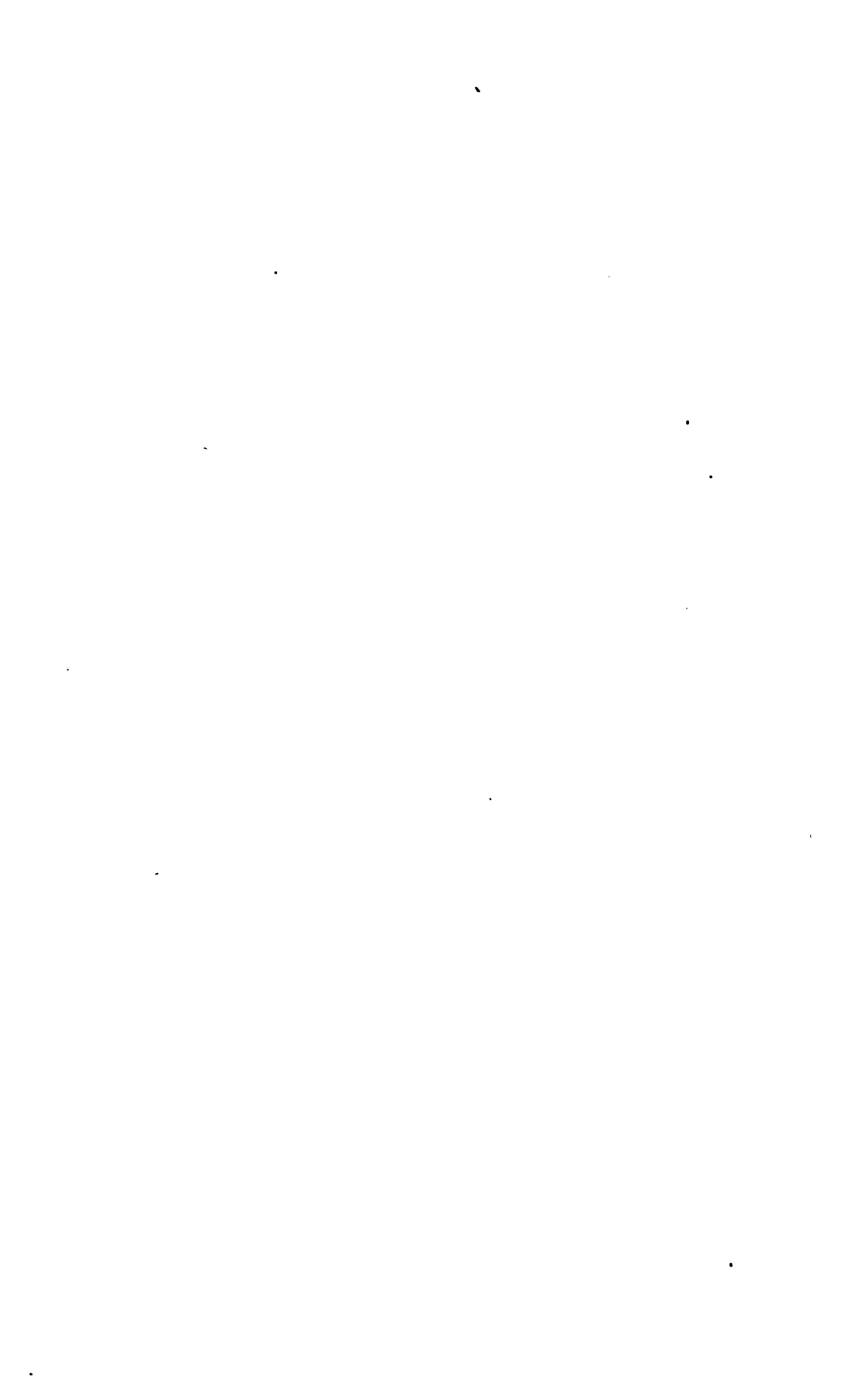
CLINICAL PATHOLOGY

CHAPTER I.

THE HEART.

The Importance of the Circulation.—The circulation is of fundamental importance to the body. It is not, of course, true, as was formerly believed, that the functions of the individual organs depend primarily upon the amount of material that they receive from the blood. Without doubt their activities depend rather upon the condition of the parenchyma cells and upon the stimuli which these receive from the nervous system.[1] Yet it is certain that, in warm-blooded animals at least, a sufficient supply of oxygen, salts, and food materials to the tissues is a necessary requisite for a normal course of life. Disturbances of the circulation are therefore of great importance, and the more complex the organ affected, the more serious are the results of such disturbances.

The Pulmonary Circulation.—A disordered condition of the circulatory system may have its origin either in the pump which propels the blood or in the tubes through which the blood flows. The right ventricle drives venous blood at a comparatively low pressure through the pulmonary vessels, which form

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[1] We are, however, now acquainted with at least one example demonstrating that the blood may normally carry a specific substance which stimulates an organ to activity,—viz., the secretin, stimulating the pancreas.—ED.

a system of short tubes, whose combined area of cross-section is very great. Through the walls of these capillaries, the interchange of gases between the blood and the air in the lungs occurs; and since this interchange takes place quite rapidly, the pulmonary system of a large number of short tubes seems best fitted for the work to be performed. The vessels play a relatively subordinate part in controlling the circulation in the lungs, for the pulmonary arteries possess little, if any, tone.[2] So far as we know, the different parts of the lungs are functionally equal, and there seems to be no necessity for a variation in the blood-supply to different pulmonary areas. During a period of rest, when only a slight interchange of gases is necessary, the rate of blood-flow in the lungs is comparatively slow; but during exercise, when larger amounts of gases must be interchanged, a great quantity of blood is propelled through the lungs. The increased respiratory movements assist the action of the heart in maintaining this more rapid circulation.

The General Circulation.—The relations are quite different in the greater circulation. Here a higher blood-pressure prevails at the onset, its height depending upon the contractions of the left ventricle, and upon the size of the smaller arteries. Variable amounts of blood may be made to pass through different organs without any alteration of the general arterial pressure, for, as the resistance to the flow of blood through one organ is lessened, the resistance to the flow through another may be correspondingly increased. Such a mechanism is of the greatest service, for here all parts are not of equal functional value, as they are in the case of the lungs, and it may be necessary to furnish one organ with a rich supply of blood at one time, and then later to do the same for another. The activity of the muscle-fibres of the smaller arteries regulate the distribution of the blood without at the same time necessarily altering

[2] Knoll, Wiener Sitzungsber. mathem. naturw. Kl., 1899, iii. p. 5.

the general blood-pressure. Indeed, this latter must not sink below a certain point if the brain and eye are to perform their functions properly.

The flow of blood in the veins is caused in part by the slight blood-pressure transmitted through the capillaries from the arteries and in part by other accessory forces. Of these, we may mention the suction exerted by the heart and the thoracic cavity, as well as the pumping effect produced by the varying pressure of the muscles and fasciæ upon those veins that are provided with valves.

The Adaptability of the Heart.—Any of the various parts of the cardiovascular apparatus may be diseased without necessarily disturbing the general circulation. This is due to the fact that this apparatus, like so many others in the animal body, possesses a compensatory mechanism. We need not regard this mechanism as the provision of a beneficent Providence, arming man against disease, nor need we regard it as a trait acquired in the struggles of the race against injurious agents. The compensatory mechanism for pathological processes is simply that which a healthy man possesses and uses in order to meet the varying physiological demands made upon the circulation.

The amount of work which the heart performs [3] may be approximately estimated if we know the volume of blood delivered at each systole, the velocity imparted to this blood, the peripheral resistance, and the number of heart-beats in a unit of time. In other words, it depends upon the size of the ventricular cavity in diastole, the number and intensity of the ventricular contractions, and the degree of constriction of the blood-vessels. The latter, in the lesser circulation, depends primarily upon the condition of the lungs, whereas in the greater circulation it depends upon the condition of the smooth

[3] B Lewy, Ztft. f. klin. Med., vol. xxxi. pp. 321, 520; O. Frank, Ztft. f. Biol., vol. xxxii. p. 428, and vol. xxxvii. p. 483.

muscle-fibres of the arteries and upon the vasomotor nerves which supply them.

During the life of a healthy individual, the blood flows at varying rates of speed,—rapidly when the cells need much oxygen or food material, slowly when this need is small. As stated above, it is possible that the blood-supply to an organ, or possibly to several organs, should vary greatly without affecting the general blood-flow. This is brought about by a contraction in one set of vessels, which contraction compensates for a dilatation in another set. Yet this compensation cannot meet all emergencies on account of the limited quantity of blood in the body. When large amounts of blood are needed in several parts of the body at the same time, they can only be furnished by increasing the speed of the general blood-stream.

We might think that propelling a larger amount of blood would not necessarily increase the work of the heart, for, as the volume of blood increased, the general blood-pressure might be so decreased that the two would counterbalance each other. As a matter of fact, however, this does not occur, and, indeed, could not occur, on account of the relations that exist between the amount of blood propelled, the general pressure, and the rate of flow. For example, if an extra supply of blood to the body were necessary, a diminution in the general arterial pressure would so reduce the difference in pressure between the arteries and the veins that the rate of flow in the capillaries would be insufficient to keep the heart supplied with fresh blood. Thus any great increase in the rate of flow is incompatible with a lessened arterial pressure, and consequently such an increased flow necessarily entails more work for the heart.

The work of the heart may be increased in another way,— viz., by increasing the peripheral resistance. The latter varies frequently and considerably even in health, for we know that the irritation of numerous sensory nerves will call forth con-

tractions of the smaller arteries and therewith increased resistance. It is theoretically possible that this increased resistance should be overcome without additional work for the heart, provided that as the resistance is increased, the amount of blood delivered is correspondingly decreased. Such a condition, however, would slow the circulation so that the body could not perform its functions properly, and, as a matter of fact, it does not occur. We may therefore say that any marked increase in the peripheral resistance necessitates more work for the heart.

The heart is the best motor known to man. It performs equally well the small amount of work necessary when a man is at complete rest, and the large amount necessitated by great exertion. It therefore possesses the power of adapting itself to the varying demands made upon it. Not every man's heart is capable of the most extreme exertion, and a tailor in a large city could hardly furnish the circulation necessary for the ascent of the Matterhorn. The weight of the muscular tissue of the heart, and with this its capabilities, bears a certain relation to the weight of the skeletal muscles. The tailor is unable to ascend the mountain mainly because his general musculature is weak. If this be improved by training, then the heart also increases in its capabilities, and usually at a more rapid rate. Indeed, a healthy heart rarely fails in any effort. It possesses extreme adaptability, and what is of greater importance, the adaptation occurs precisely at the time when it is most needed. To this fact the body owes its remarkable capacity for work. For example, when a ventricle in diastole becomes unusually filled (even up to six times its customary capacity),[4] then with the next systole, it drives out not all the blood, perhaps, but at least several times the ordinary quantity. On the other hand, if the arterial resistance be suddenly increased, it is as promptly overcome by the succeeding ven-

[4] Stolnikow, Du Bois' Arch., 1886, p. 1.

tricular contractions. There is no time lost in experimentation. The demand and the accomplishment occur together.[5] This wonderful adaptability of our heart expresses itself both in its powers of dilatation and of contraction. Thus in diastole the ventricles will readily expand and take up greater amounts of blood without a corresponding increase in their tension. Only a slight pressure is necessary to distend the heart after the first short period of suction is passed.[6] When the ventricle is nearly filled, however, the tension rapidly increases. The same occurs even though much larger amounts of blood must flow into the heart during each diastole. The elasticity of the heart muscle, which governs the resistance to the inflowing blood, must therefore vary with the amount of fluid that is to enter the heart. By means of this variation it is possible for the ventricle to receive very different amounts of blood within the same period of time.

The contractility of the heart also bears a certain relation to the amount of blood to be propelled. It also accommodates itself to the increased demand. The ventricle is therefore able to expel, almost completely, much more blood than usual, and to do this even against greatly increased resistance.

Without doubt this remarkable adaptability is a function of the muscle itself.[7] For the heart muscle, presumably free of all ganglion cells and nervous connections, possesses the above properties to precisely the same degree as does the intact organ.[8] The actual cause of the accommodation is not understood. So far as we know, the heart uses all its muscle-fibres at each contraction. The increased work, therefore, is accom-

[5] Cohnheim, Allg. Path.; v. Frey and Krehl, Du Bois' Arch., 1890, p. 31; v. Frey, Arch. f. klin. Med., vol. xlvi. p. 398; O. Frank, Ztft. k. Biol., vol. xxxii. p. 370.

[6] Hesse, Arch. f. Anat., 1880, p. 328.

[7] Ludwig and Thiry, Wien. Sitzungsber., vol. xlix. II. p. 421.

[8] v. Frey, Arch. f. klin. Med., vol. xlvi. p. 398; Krehl and Romberg, Arch. f. exp. Path., vol. xxx. p. 49.

plished, not by calling new fibres into play, but by causing the old to contract more quickly and more energetically. How is this brought about? In a skeletal muscle, poisoned by curare, the strength of the contraction depends not only upon the stimulus, but upon the weight to be lifted. If we ascribe similar properties to the heart muscle, we are led to the conclusion that the amount of distention directly regulates the force of the subsequent contraction. v. Frey rightly remarks that the response occurs too quickly to be a reflex act. " It frequently happens that the heart does not feel the increased resistance until the beginning of systole. It is then already too late for a reflex adjustment, and, if it waited for that, the next contraction would be abortive. Experience, however, shows that this is not the case. The contractions which follow immediately after an increased call upon the heart are, as a rule, unusually powerful."

Although the nervous system is not necessary for this adaptation, yet it would seem that, in many cases, both the elasticity and the contractility may be increased by nervous influences. Kauders[9] has performed a remarkable series of experiments, in which he has shown that an increased resistance, produced by an irritation of a sensory nerve (*e.g.*, the sciatic), is better overcome by the left ventricle than the same degree of resistance produced by direct compression of the aorta. In the latter case the left ventricle failed to do its work, and the pressure in the left auricle increased; whereas in the former the work was not only well done, but the auricular pressure was even diminished. The left ventricle worked here to better purpose, probably because it was favored by nervous influences from the medulla.

As has been shown above, when the peripheral resistance is increasd or when there is a demand for a greater blood-

[9] Ztft. f. klin. Med., vol. xxi. p. 61; Grossman, ibid., vol. xxvii. p. 151.

supply, the heart can only meet the new requirements by doing more work. The slightly lengthened systole, which may occur under these circumstances, and which amounts to not more than from twenty to thirty per cent., does not lessen the work sufficiently to compensate for the other factors.

The heart's capacity for work is certainly very great. Even though, experimentally, the amount of blood in the ventricles during diastole be increased sixfold, they are able to empty themselves almost completely, and a doubling of the arterial pressure does not cause serious embarrassment. Yet, on the other hand, an increase in the heart's activities is not without its disadvantages. For, in the first place, the increased work is only possible by increasing the chemical decomposition in its muscle, and, in the second, an excessive rise in arterial pressure is by no means without danger, especially if the blood-vessels are not perfectly healthy.

Hypertrophy of the Heart.—Frequent and marked increase in the work of the heart leads to secondary changes. In this respect, so far as we know, the heart acts precisely like a striated muscle. Continued exertion leads to its enlargement, owing to the increase in size and number of its muscle-fibres. It then reaches a new equilibrium, and is able to accomplish without effort tasks that formerly called its reserve force into play. Bauer [10] designates this as a " strengthening of the heart." When an increased effort is demanded of it, the work is divided among more numerous and stronger fibres, and it is therefore more easily performed. The extreme limits of accommodation have also become greater, for we may assume that the stronger hypertrophied muscle possesses a greater reserve force than the former weak muscle, and experience seems to bear out this assumption.

If the weight of the heart muscle depends upon the amount of work done, then we should expect that the weight would

[10] Festschr. f. Pettenkofer, Munich, 1893. ·

vary in different individuals.[11] In the numerous and careful observations of W. Müller,[12] and of Hirsch,[13] such a variation has been demonstrated, there being a definite relation between the weight of the heart and the total weight of living body tissue. We have no method of directly determining the amount of work that has been performed by a heart. Perhaps it would be of value to know the work done by the body as a whole, although different sorts of work affect the circulation differently. It is also difficult to determine the total weight of living tissue in a body or even that of the muscular system, which is of special importance. Thus far, statistics have dealt with the relation that exists between the weight of the heart and the total body weight, and although the latter introduces inaccuracies on account of the varying amount of fat and the presence of œdema, nevertheless the figures from a large amount of material have shown that the ratio between the weight of the heart and that of the body varies only within narrow limits; from which consideration, Hirsch concludes that the activity and weight of the body musculature exercise a determining influence upon the weight of the heart.

If this ratio of the weight of the heart to the body weight be increased, we speak of an hypertrophy of the heart. Although such an hypertrophy may arise from a variety of causes, it is questionable whether it ever results from prolonged exertion alone. We know that severe muscular exertion increases the weight of the heart, for the amount of blood to be propelled is much greater than normal and the arterial pressure is not diminished, but is usually increased.[14] Under these circumstances, the heart necessarily becomes larger, but this increase in size is not usually out of proportion to the accom-

[11] See Krehl in the Nothnagel System.

[12] Die Massenverhältnisse des menschlichen Herzens, Hamburg, 1884.

[13] Arch. f. klin. Med., vol. lxiv. p. 597.

[14] Moritz, Arch. f. klin. Med., vol. lxxvii. p. 339.

panying increase in the skeletal musculature. We possess no very exact anatomical observations on the size of the heart under such conditions. Clinical examination, however, usually fails to show any hypertrophy. Yet two observations speak in favor of the view that hypertrophy without weakness may result from prolonged overexertion. Race-horses possess relatively large hearts,[15] and skid-runners of Denmark who were apparently healthy have been shown in several instances to have hypertrophy of the left ventricle.[16] We may, therefore, say that a relative increase in the weight of the heart as a result of overexertion is a great rarity, and that, when it occurs, it is usually due to pathological changes in the muscle. We shall return to this subject in speaking of heart hypertrophy.

Valvular Disease of the Heart.—As has been said, the heart possesses the power of adjusting itself to varying circulatory conditions, which would otherwise interfere seriously with the supply of blood to the body. It exercises this power not only to meet the varying demands made upon it during health, but to compensate for the destructive processes wrought by disease.

The function of the valves of the heart is to direct the current of blood in the proper direction. In order to prevent leaks, the valves must be intact, they must be properly controlled by the papillary muscles and the chordæ tendineæ, and the openings which they close must be reduced in size by the contraction of the surrounding ring of muscle, a most important factor. The orifices of the heart become much smaller during systole, at which time they may be readily closed, whereas during diastole they are relatively too large for the valves.

The Etiology of Valvular Disease.—Diseases of the valve

[15] Friedberger and Fröhner, Spez. Path. u. Ther. der Hausthiere, 1896, vol. i. p. 503.

[16] Henschen, Mitteil, aus der med. Klin. zu Upsala, Jena, 1899, p. 53.

segments may be produced by micro-organisms or their toxins. Acute articular rheumatism and the septic diseases are the most frequent causes of valvular heart lesions. Next to these we may name typhoid fever, scarlet fever, variola, chorea, and gonorrhœa. Indeed any infectious disease may injure the heart valves.[17]

The bacteria most frequently found in acute endocarditis are the streptococci, staphylococci, and pneumococci, although other organisms, as gonococci, are occasionally present.[18] In a number of instances, as in gonorrhœal endocarditis, the heart is simply one localizing point of a general infection. In other cases, as in the acute exanthemata, the heart complications are to be regarded as the result of secondary infections. The original disease prepares the ground for the invasion of the organisms which attack the heart valves.

Not infrequently no bacteria are found in the endocardial vegetations. It is possible in such instances that organisms have been present, but that they have died out. On the other hand, such an endocarditis may possibly be produced, not by the local action of micro-organisms, but by toxins generated in some other part of the body. No micro-organisms are found, as a rule, in the endocarditides complicating carcinoma, tuberculosis, or nephritis. Not infrequently none have been found in the rheumatic endocarditis, but from other cases of this disease various bacteria have been isolated. The real cause of the heart complications of rheumatism is of considerable interest, for rheumatism is analogous in many ways to an infection with the pyogenic cocci.

Infections may attack different parts of the heart; certain ones showing a tendency to localize on the valves, others to involve more especially the myocardium. The injury to the

[17] Worobjew, Arch f klin. Med., vol. xlix. p. 466.

[18] Lenharz, Deut. med Wochenschr., 1901, Nos. 29 and 30; M. Loeb, Arch. f. klin. Med., vol. lxv p. 411.

valves begins with a degeneration of the endothelium, quickly followed by a deposit of blood-platelets and of thrombi. The tissue reaction comes later, and is more marked when the auriculo ventricular valves are affected than when the semilunar valves are diseased.

It is not our purpose to discuss the different anatomical and clinical forms of endocarditis. It suffices to recall that by ulceration and shrinkage the valves may be shortened or perforated, and that by adhesions along their margins the orifices may be narrowed. Furthermore, owing to a concomitant myocardial affection, the orifices may not be properly constricted during systole, or the auriculo-ventricular valves may not be properly controlled by the chordæ tendineæ. These latter factors are of no little importance. For example, when at autopsy we see only a slight marginal affection of the mitral valve, whereas during life there had been a decided functional insufficiency, we must regard the complicating myocarditis rather than the valve lesion as the cause of the disturbances in function.[19] No one who understands the closure of the auriculoventricular orifices can believe that such a minimal affection of the valve could possibly be the sole cause of a serious insufficiency. It is an interesting fact that the endocarditides, complicating ulcerating carcinomata and tuberculosis, are much less frequently diagnosticated than are those complicating rheumatism. Since the myocarditis is usually absent in these cases, the muscular rings contract well during systole, and the heart is less likely to be rendered insufficient from the valvular affection.

Chronic endarteritis is another important etiological factor in the production of valvular disease. This usually spreads from the aorta to the valves, but it may originate primarily in the latter.

Finally, the insufficiency may develop because the valves or

[19] Romberg, Arch. f. klin. Med., vol. liii. p. 141.

chordæ tendineæ are torn during very severe exertion, as a result of the great rise in intracardiac pressure, a very uncommon accident.[20]

The large thrombi which are sometimes found in the left auricle may hinder the flow of blood, and even produce the symptoms of a mitral stenosis. The clinical signs and symptoms so produced are not as yet well understood.

The effects of valvular lesions may show themselves in two different ways,—either the orifices are not properly closed when they should be (insufficiency), or they cannot open widely enough to allow the blood to pass through freely (stenosis). Whether, in a given case, the one or the other occurs, or, as frequently happens, both occur together, depends upon the nature of the anatomical changes present.

The seat of the disease is in part dependent upon the causative factor. The arteriosclerotic lesions most frequently affect the left semilunar valves on account of their proximity to the aorta. As a rule, a fresh endocarditis will produce an insufficiency and not a stenosis. The valvular vegetations in conjunction with the diseased heart muscle render the closure of the valves imperfect; whereas in order to produce a stenosis, a chronic inflammation with ultimate adhesions between the valve leaflets is necessary. The grade of insufficiency, or of stenosis,—i.e., the amount of blood which in the former case flows back, and in the latter is hindered from passing through the orifice,—is determined partly by the condition of the heart muscle and partly by the anatomical changes in the valves.

Muscular Insufficiency.—We have already mentioned the great importance of a proper constriction of the valvular orifices during systole by the surrounding ring of muscular tissue. A faulty constriction may entail serious consequences, and the so-called muscular insufficiencies are much more common than is generally supposed. They occur most frequently as a result

[20] M. B. Schmidt, Münch. med. Woch., 1902, No. 38.

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of myocardial disease, and in chronic myocarditis, especially, they may lead to precisely the same disturbances of function as does a shortening of the valve segments. Indeed, the diagnosis between the two is often extraordinarily difficult, and many reported instances of " healed valvular disease" are doubtless merely improved cases of myocarditis with muscular insufficiency.

Muscular insufficiencies occur much more frequently at the auriculo-ventricular orifices than at the semilunar openings. At the mitral orifice they are usually due to a faulty contraction of the surrounding ring of muscle, or possibly at times to a lack of control of the valve segments by the papillary muscles and chordæ tendineæ. On the right side of the heart the contraction of the ventricle, as a whole, is usually at fault. According to v. Jürgenson, the slow contraction of the fatigued muscle may also interfere with the closure of the valves.[21] The term " relative insufficiency" has been used for the condition in which the orifice is so widened that the valves are no longer able to close it. Although this " stretching" of the opening may, indeed, occur, we must insist that, after all, the essential factor is not the dilatation of the ring, but the faulty constriction during systole.

A relative insufficiency of the valves at the entrance to the aorta is much less uncommon.[22] At times it is due to an insufficient development of the muscle just beneath the semilunar valves, or it may originate in a dilatation of the fibrous ring at the beginning of the aorta.

Aortic Insufficiency.—It is now necessary to point out how the various valvular lesions affect the distribution of the blood in the body, and how the heart accommodates itself to the new conditions arising from the valvular defects.[23]

[21] v. Jürgenson, in Nothnagel's System.
[22] Popow, Petersb. med. Wochenschr., 1902, No. 45.
[23] Moritz, Arch. f. klin. Med., vol. lxvi. p. 349; D. Gerhardt, Arch. f. exp. Path., vol. xlv. p. 186.

When there is an insufficiency of the aortic valves, a part of the blood that is thrown into the aorta by the contraction of the left ventricle returns again into that cavity during diastole. The amount that flows back is determined by the size of the pathological opening left by the improper closure of the valves, by the difference between the pressure in the aorta and that in the ventricle, and by the duration of diastole. An increased heart-rate, which shortens more especially the diastolic period, should be of advantage in aortic insufficiency since it lessens the amount of the leak backward. Clinically, a rapid heart action is not infrequently found associated with this lesion,[24] but we are ignorant of its cause. The walls of the ventricle are very flabby during diastole, so that they are easily stretched by the stream of blood flowing in under high pressure from the aorta. This leads to a dilatation of the ventricular cavity, and the amount of dilatation depends upon the quantity of blood which flows back and upon the degree of elasticity of the muscle wall. In early diastole the ventricular wall is particularly flabby, as the filling proceeds it becomes more tense, and toward the end of diastole the tension increases rapidly. By thus increasing the resistance to the inflowing blood the ventricle can protect itself against overdistention. We have already seen that this resistance varies normally according to the varying amounts of blood which must be delivered, and that the ventricular wall becomes more distensible whenever larger quantities of blood must be propelled (p. 267). The abnormal filling of the ventricle in aortic insufficiency may or may not act as a hinderance to the entrance of blood from the auricle. Whether the one or the other occurs depends mainly upon this variation in the elasticity of the ventricular musculature. If this change, so as to accommodate the extra amount of blood, then it is possible that the auricle will empty itself as usual and that there will be no disturbance in the flow of blood from the

[24] Levy, Ztft. f klin. Med., xxxi. p. 539.

lungs.   Such cases do occur, and have been observed both clin-
ically and experimentally.[25]

On the other hand, many patients with aortic insufficiency
show symptoms referable to a damming back of blood into
the lungs.   Their dyspnœa and the marked accentuation of the
second pulmonic sound are indicative of increased pressure in
the pulmonary circulation.   It is easy to understand how this
might be brought about by an uncomplicated aortic regurgita-
tion.   It is only necessary for the tension of the ventricular
wall to increase before all the blood from the lungs had entered
the ventricle.   This would hinder the entrance of blood from
the auricle and would tend to produce a pulmonary congestion.
Furthermore, the suction of blood from the lungs due to the
expansion of the ventricle in early diastole may also be dimin-
ished owing to the stream entering from the aorta.   We have
both clinical and experimental evidence that under such cir-
cumstances a pure aortic regurgitation may cause a stasis of
blood in the lungs.[26]

In spite of its increased contents, the left ventricle in aortic
regurgitation empties itself in about the same length of time
as does the normal ventricle, although according to recent
observations [27] it may not empty itself so completely.   For
there is evidence that the blood is not usually entirely expelled
during systole if the ventricular cavity be greatly dilated.   This
fact, however, is really of no great importance in the matter
under consideration, for so long as the ventricular muscle is
efficient, the residue of blood left in the cavity at the end of
systole is insignificant compared with that which streams back
from the aorta during diastole.

In a series of classical experiments, Rosenbach[28] has shown

[25] Kornfeld, Ztft. f. klin. Med., vol. xxix. pp. 91, 344, 450.

[26] Kornfeld, loc. cit.; Romberg and Hasenfeld, Arch. f. exp. Path., vol.
xxxix. p. 333.

[27] Johanssen and Tigerstedt, Skan. Arch. f. Phys., vol. i. p. 331.

[28] Arch. f. exp. Path., vol. ix. p. 1.

that after artificially puncturing the aortic valves of a dog, all the symptoms of an insufficiency occur without any marked lowering of the mean arterial pressure. Since then this experiment has been frequently repeated, but with varying results. In rabbits the mean pressure is usually lowered as a result of the operation, whereas in dogs it may remain normal, be lowered, or even be raised. These variable results probably depend, in the first place, upon the strength of the heart, and, in the second place, upon the severity of the lesion. The rabbit's weak heart cannot so readily compensate for the injury, and its blood-pressure sinks. The dog's stronger heart readily overcomes a slight injury (*e.g.*, puncture of the valve by a rod); whereas a more serious one (*e.g.*, tearing off a valve) results in a lowered mean blood-pressure. It is possible that nervous reflexes may play some part in maintaining the blood-pressure in these cases, especially when the injury to the valves is sudden. The principal factor, however, is undoubtedly the accommodation of the heart muscle itself.

All our experience goes to prove that a muscle will hypertrophy if it does an increased amount of work over a long period of time. We should expect the same rule to apply to individual parts of the heart, and especially so since their work is not limited to eight or ten hours a day, but is continuous, day and night. The work of the left ventricle is increased in aortic insufficiency, for it must propel not only the blood which enters from the auricle, but, in addition, that which leaks back from the aorta during each diastole. The total amount expelled is therefore increased, while the pressure against which it is expelled is but little changed. Practical observations have shown that in aortic insufficiency there is always an hypertrophy of the left ventricle with a dilatation of its cavity. The cavity is dilated on account of the abnormal amount of blood which it must accommodate, and the walls hypertrophy because of the extra work thrown upon them. If the conditions

for an increased pressure in the left auricle, as described above (p. 26), are present, then its work and the work of the right ventricle are also increased, and hypertrophy of these two parts of the heart results.

Unfortunately we possess no exact anatomical data concerning these last points. The thickness of the heart wall at autopsy is greatly influenced by the condition of the heart when it stopped beating, whether it was in systole or diastole, so that we cannot judge from such measurements as to whether such slight hypertrophy as would occur in the left auricle and the right ventricle in cases of aortic insufficiency was present or not. Perhaps the employment of W. Müller's method will throw more light on the subject.[29]

It is often erroneously stated that every aortic insufficiency is accompanied by a considerable, and easily demonstrable, enlargement of the left ventricle. When the muscle is efficient, the degree of dilatation and hypertrophy is directly dependent upon the amount of blood which regurgitates from the aorta. If a third or fourth of the volume driven out leaks back, it necessarily leads to a considerable dilatation and hypertrophy. If, however, only a few cubic centimetres flow back, it is possible that the lesion can be readily diagnosticated clinically from the characteristic murmur, but that the hypertrophy and dilatation of the left ventricle will be so slight that it is quite impossible for the physician to detect it by physical examination.

Aortic Stenosis.—In stenosis of the aortic orifice the flow of blood from the left ventricle into the aorta is impeded. It is probable that under physiological conditions this orifice is not round and large during systole, but that it is encroached upon by the contraction of the muscle which surrounds it and which is an extension upward of the ventricular musculature. The

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[29] W. Müller, Die Massenverhältnisse des menschlichen Herzens, Hamburg, 1884.

blood flows smoothly up to the contracted portion and then out into the wider aorta. Under ordinary conditions, the delicate semilunar valves are easily thrust aside. If, on account of disease, they become stiff and rigid, then they hinder the escape of blood more or less. The ventricle must therefore work against a greater resistance. The prolongation of the ventricular systole, which may be from seven to thirty per cent. longer than normal,[80] is by no means proportionate to the increased resistance. The lesion, therefore, causes a greater amount of work to be thrown on the left ventricle. As a result of this extra work, we always find an hypertrophied left ventricle in cases of aortic stenosis. At first, there is no dilatation of its cavity, and the auricle, lungs, and right heart are entirely unaffected. A dilatation will only occur when the heart muscle can no longer accomplish the additional work, either because the obstruction has become too great, or because the muscle itself is weakened.

Mitral Stenosis.—Lesions at the mitral orifice produce more complicated conditions than those at the aortic, because they lead to changes in the lungs and in the right heart.

In mitral stenosis [81] there is a hinderance to the flow of blood from the left auricle into the left ventricle. When the auricle contracts, it must overcome a greater resistance, and this additional work leads to an hypertrophy of its musculature. On account of the thin walls, however, its capacity for increased work is very limited, so that a dilatation occurs much earlier than in the case of the ventricle. An important factor contributing to this dilatation is the increased pressure which prevails in the pulmonary veins. At each systole of the auricle, an unusual proportion of its contents is forced back into the pulmonary veins owing to the obstruction in front at the mitral orifice. During diastole, therefore, the blood from the lungs

[80] Lüderitz, Ztft f. klin. Med., vol. xx. p. 374.
[81] D. Gerhardt, Arch. f. exp. Path., vol xlv. p. 186.

enters the auricle with more than ordinary force, the diastolic pressure in the auricle is increased, and, owing to the diminished muscular tonus during this period, the cavity becomes dilated.

The abnormal pressure in the pulmonary veins is transmitted through the short and relatively wide capillaries of the lungs to the pulmonary artery. Everything now depends upon the behavior of the right ventricle, which is placed in much the same position as is the left ventricle in a case of aortic stenosis. The pressure in the pulmonary artery must be maintained at a higher level than usual, in order to maintain the difference in pressure between the artery and vein, and consequently the flow of blood through the lungs. We recognize this increased pulmonary pressure clinically by the accentuation of the second pulmonic sound. The extra work necessitated by this high pressure is thrown upon the right ventricle and leads to its hypertrophy.

The effect of mitral stenosis upon the left ventricle depends entirely upon the amount of blood that the latter receives. When the stenosis is slight and the right heart maintains the necessary pressure in the pulmonary system, the left ventricle is not affected, for it receives its customary supply of blood. If, however, the right heart cannot compensate for the obstruction present, then the left ventricle is not filled to the normal amount, its work is diminished, and its muscle atrophies. This reasoning has been confirmed by the findings at autopsy. In pure mitral stenosis, the left ventricle is either normal or atrophied. If at times an hypertrophy of the left ventricle has been found, it is to be attributed to an associated mitral insufficiency, present or past. The two lesions are very frequently combined, and this naturally modifies the resulting anatomical changes.

Mitral Insufficiency.—The conditions present in mitral insufficiency are very similar to those in mitral stenosis. A part

of the contents of the left ventricle is thrown back into the auricle during systole, and the degree of insufficiency may be measured by the amount of blood which takes this backward course. The lungs and the right heart are affected precisely as in the case of mitral stenosis. The left auricle becomes dilated and hypertrophied, the blood-pressure in the pulmonary system is raised, and the right ventricle must pump against an increased resistance. The amount of blood delivered may, indeed, be decreased, but not enough to neutralize the effects of the increase in pressure. The work of the right ventricle is therefore usually increased, and correspondingly we ordinarily find an hypertrophy of this part of the heart at autopsy.[32]

During diastole the blood flows into the left ventricle with unusual force, owing to the increased pressure in the auricle and the pulmonary veins. The amount that flows in must also be greater than normal if the body is to receive its customary supply of blood, for with each contraction of the left ventricle a certain proportion of its blood does not pass into the aorta, but is thrown back into the auricle. It is therefore necessary for the ventricle to pump more blood than usual, and we have no reason to believe that it does so against a lessened resistance, for the leak is hardly large enough to bring that about. The increased work performed by the left ventricle leads to its hypertrophy, a condition always present in mitral insufficiency. The ventricular cavity also becomes dilated owing to the larger quantity of blood which it receives during diastole. Thus, hypertrophy and dilatation of the left ventricle go hand in hand. The combination is of advantage not only in propelling the blood, but probably also in drawing it from the auricle and from the lungs during diastole.

Valvular Lesions of the Right Side of the Heart.—Valvular lesions of the right side of the heart give rise to secondary

[32] Moritz, Arch. f. klin. Med., vol. lxvi. p. 421.

changes, very similar to those which take place on the left side under similar conditions. We must remember, however, that the musculature of the right ventricle is relatively weak, and that it is not capable of the same degree of accommodation as is that of the left ventricle; furthermore, that there is no powerful ventricle directly behind the tricuspid orifice to compensate for its disabilities. The valves of the right side of the heart are not infrequently diseased during the fetal period. Although the tricuspid valve is but rarely the seat of a verrucose inflammation in later life, a relative insufficiency of the tricuspid orifice is no uncommon sequel to valvular disease of the left heart. Disease of the pulmonary valves, developing during adult life, is a great rarity.[88]

During fetal life, micro-organisms in the blood-stream usually injure the valves of the right side of the heart, whereas in extra-uterine life the left side is the one which is more frequently affected. One is tempted to explain this remarkable fact by the relative amounts of work done by the two sides or by the influence of aërated blood, since in fetal life it is the right side which receives the aërated blood. We have no proof, however, for either of these two hypotheses. A fetal endocarditis is not uncommonly associated with congenital malformations, such as septum defects, transposition of the arteries, or persistence of the Ductus Botalli. Possibly the malformations diminish the resistance of the endocardium to infectious agents. The most important of the congenital heart lesions is pulmonary stenosis. This stenosis, which may be situated either in the neighborhood of the valves or at the conus arteriosus, leads to hypertrophy of the right ventricle precisely as an aortic stenosis leads to hypertrophy of the left.

Combined Valvular Lesions.—The effects of valvular disease may be best studied when there is a simple stenosis or insufficiency of a single valve, and when no complications are

[88] Geigel, Münch. med. Wochens., 1897, No. 9.

present. Yet such simple cases are rare. In the right heart we frequently find associated defects in development; in the left heart, combinations of several valvular lesions. Pure mitral insufficiency is comparatively frequent, but uncomplicated cases of mitral stenosis, or of aortic insufficiency, or of aortic stenosis, are much rarer than are the combinations of mitral insufficiency with mitral stenosis, aortic insufficiency with aortic stenosis, or aortic insufficiency with double mitral disease. The aortic semilunar valves are closely adjacent to the aortic segment of the mitral valve, and when the latter is diseased the former are also frequently affected.

The effect of a combination of valvular lesions is the resultant of the effects of the individual lesions. They may even tend to neutralize each other, so that the combination is less harmful than the individual lesions. For example, the dilatation of the left ventricle resulting from aortic insufficiency may be lessened by an associated aortic stenosis; and although both mitral insufficiency and mitral stenosis produce similar effects in damming the blood back into the lungs, they tend to neutralize each other so far as their effect upon the left ventricle is concerned. Indeed, we may say in general that the stenosis which so often follows a valvular insufficiency may be of advantage in that it may limit the amount of blood which regurgitates. Caution must be used, however, in deciding this question in the individual case, for other factors, especially the condition of the heart muscle, are often of paramount importance.

Hypertrophy of the Right Ventricle.—The work of the right ventricle is directly dependent upon the condition of the pulmonary circulation. Anything that increases the pressure in the pulmonary vessels increases the resistance against which the right ventricle must force the blood. We have seen an illustration of this in the case of mitral valve disease. Similar effects may result from a weakened left ventricle which can-

not completely empty itself during systole.   Its power of
suction in early diastole is also diminished, for this power de-
pends upon the elastic rebound after a powerful contraction,
or possibly upon an active process in the muscle-fibres them-
selves.[34]   The unexpelled blood in the ventricle and the lessened
suction hinder the entrance of blood from the lungs, raise the
pressure in the pulmonary circulation, and so increase the work
of the right ventricle.   We have seen that the left ventricle can
alter its elasticity under certain circumstances so that it can
hold a larger amount of blood in each diastole, and the ques-
tion naturally arises, Why does not the weakened ventricle do
this instead of damming the blood back into the lungs?   The
reason seems to be that the muscle tissue is so diseased that
its elasticity as well as its contractility is diminished.

Primary disturbances of the circulation in the lungs may
likewise affect the right heart.   We know that the resistance to
the blood-flow in the pulmonary vessels is normally very slight.
Large vascular areas, up to three-quarters of the total, may be
thrown out of function, and yet a sufficient amount of blood
may be sent through to the left ventricle.[35]   The right heart
simply propels the blood through the remaining pulmonary
vessels at a higher rate of speed.   The open vessels are, in-
deed, dilated, but not sufficiently to compensate for the others
thrown out of function, so that the pressure in the pulmonary
artery rises.   The dilatation of the vessels remaining open is
quite different from that which takes place under correspond-
ing circumstances in the greater circulation.   In the latter,
when a vessel is closed, the general pressure does not neces-
sarily rise, because vasomotor influences may produce a com-
pensatory vascular dilatation in other parts of the body;   in
the lungs, the resulting dilatation is purely passive, and is
due to the increase of pressure in the pulmonary artery caused

[34] Brauer, Kongress f. inn. Med., 1904.
[35] Lichtheim, Die Störungen des Lungenkreislaufes, Berlin, 1876.

by the obstruction in one of its branches. This increased pressure necessitates an increase in the amount of work done by the right ventricle, which will be greater or less in any given case, depending upon the number and dilatability of the pulmonary vessels remaining open. In case the increased work persists for some time, hypertrophy of the right ventricle will ensue.

For this reason the right ventricle becomes hypertrophied as a result of sclerosis of the pulmonary artery (a rare condition) ; [36] also in those more frequent pulmonary diseases which lead to destruction or compression of the vessels, such as cirrhosis of the lungs from various causes, chronic pneumonia, pulmonary emphysema, and thoracic deformities.[37] Long continued bronchitis is often described as a cause of hypertrophy of the right ventricle, and especially as a cause of the enlarged right heart found in children, who are subjects of this disease. It is difficult to say whether the bronchial inflammation directly increases blood-pressure or whether the continual coughing gives rise to the hypertrophy of the right ventricle by its effect on the intrathoracic pressure.

It has often been asserted that we have in tuberculosis an exception to the general rule that chronic pulmonary disease leads to hypertrophy of the right ventricle. To account for this supposed exception, numerous explanations have been offered, one of which is to the effect that the total quantity of blood is diminished in this disease. We now know, however, that tuberculosis is no exception to the general rule. Anatomical investigations have shown that, in proportion to the body weight, the weight of the right ventricle is increased in a large proportion of those who die of consumption.[38] Clinical evidence supports the same view, for it is not uncommon

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[36] Romberg, Arch. f klin. Med., vol. xlviii. p. 197.

[37] Hirsch ibid , p 328.

[38] Hirsch, loc. cit

to find an accentuation of the second pulmonic sound during life in tuberculous patients.

Extensive pleuritic adhesions may also lead to an hypertrophy of the right ventricle.[89] Their interference with the movements of the lungs doubtless deprives the pulmonary circulation of the assistance usually derived from these movements, so that additional work is thrown on the right ventricle.

Hypertrophy of the Left Ventricle.—The work of the left ventricle is made greater by any increase in the resistance to the flow of blood through the peripheral arteries. A temporary increase in resistance, arising from vasomotor influences, is not an uncommon physiological occurrence.

Of considerable importance as a cause of permanent increase in the arterial pressure are certain forms of arteriosclerosis.[40] When the elasticity of the arteries is diminished, they offer a greater resistance to dilating forces; but once having been dilated, they do not so easily recover their original size.[41] Various opposing factors must therefore be considered. The rigidity of certain areas may be neutralized by dilatation of other areas. There is also a tendency for the affected vessels to become permanently dilated. The precise effect of these various opposing factors can only be determined by experimental investigations. Hitherto we have had no method of experimentally inducing the disease, but since arteriosclerosis has recently been produced by the injection of adrenalin chloride into animals,[42] we may expect important developments in this field of research in the near future.

As a matter of fact, hypertrophy of the left ventricle develops in only a small proportion of patients with uncom-

[89] Bäumler, Arch. f. klin. Med., vol. xix. p. 471.
[40] Kongress f. inn. Med., 1904.
[41] Israel, Virch. Arch., vol. ciii. p. 461.
[42] W. Erb, Kongress f. inn. Med., 1904.

plicated arteriosclerosis. It is present especially in cases of sclerosis of the first part of the aorta, and in extensive sclerosis of the splanchnic vessels.[43] The splanchnic arteries are of such paramount importance in controlling the peripheral resistance that when they are diseased it is difficult or impossible to attain compensation by a dilatation of other vascular areas. Other uncomplicated cases of arteriosclerosis rarely show any marked degree of heart hypertrophy.

Various complications often render it extremely difficult to estimate the effect of arteriosclerosis upon the heart. The same cause that induces the disease of the arterial walls may also independently act upon the heart muscle. As examples of such causes, we may name the excessive use of alcoholic drinks, of coffee, and of tobacco, severe and continued exertion, infectious diseases, and, above all, syphilis. Then, too, arteriosclerosis itself may lead to degeneration of the heart muscle owing to an involvement of the coronary arteries. Finally, an associated chronic nephritis may produce an hypertrophy of the heart. We thus see how extremely difficult it is, in an individual case, to determine whether the arteriosclerosis is the direct cause of the heart hypertrophy or whether the latter is due to some associated complication.

The left-sided hypertrophy accompanying aneurism of the aorta is to be ascribed to some complicating condition. It is difficult to see how a dilatation of the vessel would increase the work of the heart, and, as a matter of fact, we do see patients with aneurisms in whom there is no enlargement of the left ventricle. When the latter occurs, we may usually ascribe it to the arteriosclerosis present or to an associated aortic insufficiency.

Hypertrophy of the left ventricle may result from that rare condition, congenital stenosis of the aorta. Such a narrowing would increase the work of the heart by offering a greater

[43] Romberg and Hasenfeld, Arch. f. klin. Med., vol. lix. p. 193.

resistance to the blood-flow. In this condition, the hypertrophy may not develop until late in life. If such be the case, we may assume that the stenosis produced but little effect so long as there were no great demands upon the heart, but that the hinderance made itself felt when a more active circulation was rendered necessary by the exertion of later life.

Severe dyspnœa causes a marked rise in blood-pressure, and it has long been a question whether moderate dyspnœa continued over a long period of time may not give rise to hypertrophy of the left ventricle. From recent observations,[44] we know that persons with such chronic dyspnœa do show an unusually high arterial pressure, and there is reason to believe that this may ultimately produce an hypertrophy of the left ventricle.

Hypertrophy of Both Ventricles.—Hypertrophy of both ventricles is produced by causes that increase the work of both. Pericardial adhesions with mediastinitis are usually reckoned among such causes, and it is easily conceived that these conditions might throw extra work upon the heart, which must now move surrounding structures, even the chest wall, with each contraction. As a matter of fact, we frequently find heart hypertrophy associated with chronic pericarditis. It is, however, questionable whether any causal relation exists between the two, for in some cases no hypertrophy is present, and, indeed, the heart may be atrophied. Since pericarditis is often associated with disease of the heart muscle, the cases that show hypertrophy should be studied with especial regard for the effect which these myocardial changes may have had in the production of the hypertrophy.

It is theoretically possible that an increase in the number of beats per minute might lead to hypertrophy of the heart. Such an increased heart-rate is seen in nervous people, especially in association with exophthalmic goitre. We often have the

[44] Hensen, Arch. f. klin. Med., vol. lxvii. p. 479.

impression that the heart contractions are also more forcible in this disease, and it has been shown that the blood-pressure is frequently above the normal.[45] The conditions necessary to produce an hypertrophy are therefore present, and, as a matter of fact, it is not uncommon to find enlargement of the heart accompanying exophthalmic goitre. It is, however, questionable whether this hypertrophy is due to the rapid heart action or whether it is due to the direct action of toxic substances. In some cases of rapid heart action, the hypertrophy, if present at all, is very slight, probably because the rapid beating does not continue for any length of time.

Cardiac Changes in Renal Disease.—The changes in the heart that follow disease of the kidneys are very difficult to explain. In a great number of cases of acute and chronic nephritis there is an increase in the arterial pressure. If this increase in pressure lasts for more than four weeks, an hypertrophy of the heart develops.[46] It follows, therefore, that heart hypertrophy occurs more frequently in chronic than in acute nephritis. In the endeavor to explain this rise of pressure and the concomitant hypertrophy, we must first know what parts of the heart are affected. According to v. Bamberger's statistics,[47] the left ventricle alone is enlarged in about half the cases, while in a somewhat smaller number both ventricles are involved. These figures, however, are based upon the apparent size of the heart or upon measurements of the thickness of the muscular wall, disregarding the question as to whether the heart stopped in systole or diastole and disregarding also the relation of the size of the heart to the total weight of the body. Accurate figures can only be obtained by weighing the different parts of the heart according to the method of W. Muller. In fourteen cases of chronic

[45] Hochhaus, Deut. med. Wochens., 1900, No. 44.
[46] Friedlander, Arch. f. Phys., 1881, p 168.
[47] Volkmann's klin. Vort., No 173.

nephritis studied by this method[48] every portion of the heart, auricles and ventricles, were found hypertrophied, in the great majority of cases, the left ventricle being most affected. These observations, in spite of the small number of cases, are of great value on account of their accuracy. Clinically we frequently hear an accentuation of the second pulmonic sound in cases of chronic nephritis, an indication of increased pressure in the pulmonary circulation which would ultimately result in hypertrophy of the right ventricle.

Not all diseases of the kidney induce heart hypertrophy. It is frequently absent in the nephritides produced by toxic agents, such as arsenic and phosphorus, and in those associated with certain infectious diseases, as diphtheria and typhoid fever. In primary acute Bright's disease, which is probably infectious in character, and in the nephritis secondary to scarlet fever, there is practically always an increase in the arterial pressure. Chronic interstitial nephritis is always accompanied by an enlargement of the heart, frequently of the most extreme grade. In the so-called chronic parenchymatous nephritis, hypertrophy of the heart is present in about half the cases.[49] There are no changes in the heart in pure cases of amyloid kidney. It is important to note that when obstruction to the flow of urine leads to renal disease, as from calculi or abdominal tumors, the heart frequently undergoes hypertrophy.

Any attempt to explain the heart hypertrophy that accompanies diseases of the kidney must start from the fact that there is an increased arterial pressure. This appears before the hypertrophy. A rise of blood-pressure, amounting to fifty millimetres of mercury, has been observed within forty-eight hours after the onset of an acute nephritis.[50] The accentua-

[48] Hasenfeld, Arch. f. klin. Med., vol. lix. p. 210; Hirsch., ibid., vol. lxviii. p. 74.

[49] Buttermann, Arch. f. klin. Med., vol. lxxiv. p. 1.

[50] Buttermann, loc. cit.

tion of the second pulmonic sound in many cases allows us to infer a corresponding rise of pressure in the pulmonary circulation. As has already been stated, this inference is borne out by anatomical investigations, for in eighty-two per cent. of cases examined by modern methods, hypertrophy was present in all divisions of the heart, and in the fourteen per cent., in which only the left ventricle was apparently affected, so much œdema was present that a slight hypertrophy of the right side of the heart might not have been demonstrable on account of the great weight of the body. It is possible that the hypertrophy of the left ventricle is more pronounced in the early stages of nephritis, and that it extends to the rest of the heart later. At any rate in the great majority of cases of chronic nephritis, the heart, if affected at all, is affected in its entirety, and any explanation of the cause of the hypertrophy must take this fact into consideration.

One view held is that the left ventricle is primarily affected and the rest of the heart is only secondarily involved. The older explanations of such a condition—viz., that it is due to the increased filling of the coronary arteries or the intimate connection between the two sides of the heart—are absolutely without foundation. Another possibility—viz., that an incompetency of the left ventricle leads to general hypertrophy of the heart—is not so easily discovered, and needs further investigation. With the present data, however, I am disinclined to accept such an explanation.

What causes the hypertrophy of the heart and the increase in arterial pressure? Two possibilities present themselves,—a primary increase in the activity of the heart or a primary rise in the peripheral resistance. We have no grounds for believing that the former possibility plays any great part in the causation of the heart hypertrophy of nephritis. In uncomplicated cases, the rate of the heart is not changed, the amount of blood propelled at each beat is not increased, for

no dilatation of the ventricles exists, and it has not been shown that the blood is expelled from the ventricle at a higher rate of speed; *i.e.*, the period of systole is not shortened. Even were there a primary increase in the heart's activities, it would not be clear why the arterial pressure should be raised, for a dilatation of the vessels might counteract any such effect, as probably does happen in some cases of exophthalmic goitre.

The second possibility, that the rise of pressure is due to increased peripheral resistance, seems almost certain. According to Cohnheim's famous theory, the inflammation of the kidney opposes a resistance to the flow of blood through it, and in order to increase this flow the general blood-pressure is raised by a general contraction of the arterioles outside of the kidney. This theory is no longer tenable, because it fails to explain the hypertrophy of the right ventricle and because of other purely physiological reasons. A general decrease in the caliber of the blood-vessels would explain everything, for even a slight diminution, either in all the vessels or in the more important vascular areas, would greatly increase the work of the heart, since this varies inversely as the fourth power of the diameter of the combined vessels. Such a change of diameter, if present, must take place within a short space of time, as in acute nephritis; and must last for years, as occurs in chronic interstitial nephritis. Furthermore, it must affect both the general and the pulmonary vessels. Although a contraction of the smooth muscle of the smaller arteries might well explain the rise of pressure in acute nephritis, it is hardly conceivable that this should be maintained during the long course of a chronic nephritis. On the other hand, inflammatory processes might lead to a permanent narrowing of the blood-vessels. Such inflammations have, in fact, been described,[51] yet the findings are

[51] Johnson, Med-chir. Trans., vols. xxix., xxx., xxxiii., xlii., and li.; Gull and Sutton, ibid., vol. xxxiii.; Sotnitschewsky, Virch. Arch., vol. lxxi. p. 453.

inconstant and they have frequently been missed in acute nephritis, even though heart hypertrophy was present.

Finally, as a cause of the heart hypertrophy, we might conceive that an increased friction in the flow of blood would produce a rise of blood-pressure. Here, again, direct observations fail to support the theory; nephritic blood does not show a greater viscosity than normal blood.[52]

No explanation, therefore, thus far given for the heart hypertrophy accompanying renal disease, is free from objection. Personally I am inclined to locate the primary cause of the increased pressure in changes affecting the blood-current in the smaller arteries, and I should recommend a renewed study of these vessels, especially in cases of acute nephritis. Minimal changes here might entail serious consequences, for, as has been said, the work of the heart varies inversely as the fourth power of the diameter of the vessels.[53]

The " Athlete's Heart."—As has been previously stated, severe muscular exertion ordinarily increases the weight of the heart in the same ratio as it increases the weight of the general musculature. It is frequently assumed, however, that hypertrophy of the heart may result from prolonged muscular exertion. Such a relative increase in the heart's weight does perhaps occur in individual cases without there being any impairment of function, but this is certainly exceptional (see p. 30.) When overactivity affects the heart, it usually does so by causing a primary weakness of the muscle; yet here again it may be frequently questioned whether this weakening should not be attributed rather to some other associated causal agent, such as the excessive use of alcoholic liquors, arteriosclerosis, or renal disease. Further observations upon these questions are therefore necessary.

[52] Hirsch and Beck, Arch. f. klin. Med., vol. lxix. p. 503; vol lxxii. p. 560.

[53] Lewy, Pfluger's Arch., vol. lxv. p. 47.

The " Beer Heart."—It is not uncommon to find weak
hearts with an hypertrophy of the muscle and a dilatation of
the cavities in men who have been accustomed to drink very
large quantities of beer. Such hearts are most frequently
seen in Munich,[54] and may show extreme grades of hyper-
trophy. Excessive wine-drinkers occasionally suffer from a
similar condition, whereas drinkers of more concentrated alco-
holic liquors are only very rarely affected in this way.[55] They
tend to develop cardiac weakness unassociated with hyper-
trophy. In many beer-drinkers no other etiological factor is
present except the immoderate use of beer. The majority,
however, do very heavy work and consume large quantities
of food in addition to their beer. Some also have diseased
kidneys, although we are not yet certain as to whether these
are secondary to the hypertrophy of the heart or not.

The cause of the enlargement of the heart in beer-drinkers
has been ascribed by some to an increase in the total amount
of blood, a genuine plethora.[56] A larger amount of blood,
however, does not necessarily produce a rise in arterial
pressure. It is claimed by others that the quantity of blood
thrown out at each systole is increased in these patients,[57] and
that this increases the heart's work. Such an explanation has
much in its favor, but we cannot regard it as established, espe-
cially since not all beer-drinkers acquire a heart hypertrophy.
Personally I have observed these heart changes in brewers,
laborers, and students who drank immoderately, and who also
did heavy work or took violent exercise. A number of such
people certainly give the impression of being " full-blooded."
It seemed to me that the combination of beer-drinking with

[54] Bollinger, Arbeiten aus dem path. Institut zu München, 1896; Rieder,
Arch. f. klin. Med., vol. lv. p. 8.

[55] Aufrecht, Arch. f. klin. Med., vol. lvi. p. 615.

[56] Bollinger, loc. cit.

[57] Tigerstedt, Skan. Arch. f. Phys., vol. iv. p. 241.

heavy work is responsible for the heart condition. One gets the impression, furthermore, that both the dilatation and the hypertrophy may disappear if the patient changes his manner of living.

Gourmands may at times acquire a similar heart condition probably from the large amounts of food and of wine, the heavy smoking, and the not infrequent sexual excesses. In such cases the picture is often complicated by arteriosclerosis, nephritis, and myocarditis.

The Heart in Pregnancy.—It has been frequently asserted, especially by French observers, that there is an enlargement of the heart during pregnancy. As a matter of fact, in pregnancy, as in other conditions associated with a high position of the diaphragm, the area of cardiac dulness is enlarged because the heart approaches the chest wall. It has, however, been proved with all certitude that pregnancy exercises no effect on the heart other than that which could be explained by the general increase in the weight of the body.[58]

The Ability of the Heart to Hypertrophy.—-It may be asked, what conditions influence the power of the heart to hypertrophy? We may mention three factors. In the first place, the rapidity with which new demands are made on the heart. If, as usually occurs, the work is gradually increased, then the heart has time to hypertrophy gradually and to attain ultimately an enormous size and greatly increased working capacity. In the second place, the degree of hypertrophy is influenced by the amount of new work required. The more work the heart does, the greater is the resulting hypertrophy. As has been said, an enormous increase in work may be accomplished, provided the new demands are gradually increased. Yet even sudden calls upon the healthy heart are well responded to up to a certain limit. We can give no definite figures for this limit in man, but we know from clinical experience that it

* Hirsch, Arch f. klin. Med , vol. lxiv p 597.

is not a low one. Experimentally it has been shown that the heart of a large healthy dog is able to pump six times the customary quantity of blood, and to overcome three times the usual blood-pressure.

The third and most important factor that influences the heart's capacity to hypertrophy is the condition of the cardiac muscle. Without a healthy muscle, the heart cannot accommodate itself to an increase in work. The general nutrition of the body is of comparatively little significance, for Tangl[59] has shown that, even in the most emaciated animals, hypertrophy of the left ventricle will develop after an artificial valvular lesion. We have no right, therefore, to attribute a lack of hypertrophy to the poor general nutrition of the patient. It is to be attributed solely to the fact that there has been no increase in the heart's work. When additional work is required of the heart, there are only two possibilities,—either it responds and hypertrophies, or it weakens. It is, of course, probable that when the body is well nourished the heart is better able to respond, and is less likely to weaken. We may mention here that in childhood the heart possesses far greater powers of adaptation than in later life, and that it is then able to compensate to a very marked degree.

Concentric and Eccentric Hypertrophy.—The heart hypertrophies, discussed thus far, may be divided into two general classes, according to the size of the ventricular cavities. When the muscle increases without any enlargement of the cavity, we speak of a simple (concentric) hypertrophy. On the other hand, the size of the cavity may also increase, and such a condition is called an eccentric hypertrophy. This division is applicable only to hearts which are properly maintaining the circulation. As soon as they fail in this, dilatation of a totally different nature occurs, which shall be discussed later.

[59] Virch. Arch., vol. cxvi. p. 432.

The ventricular cavity must become dilated during diastole whenever it is necessary to pump more blood at each beat. Whether the cavity is also dilated in systole or not, depends upon the completeness with which the ventricle empties itself. Experimental evidence would lead us to the belief that an incomplete expulsion of the blood is by no means infrequent. In heart-failure this is the rule, and even when the heart is maintaining a good circulation it does not empty itself completely when very large amounts of blood must be propelled, or when the resistance is much increased.[60]

So long as compensation is good, it is rare for the right ventricle to become dilated as a result of increased pressure in the pulmonary circulation. The same is true of the left ventricle in cases of arteriosclerosis and nephritis. In other words, the hypertrophy in these conditions is usually of the concentric variety. On the other hand, the hypertrophy resulting from aortic or mitral regurgitation, from excessive exertion, or from the immoderate use of beer, is usually associated with dilatation of the cavity; it is an eccentric hypertrophy. It is necessary to be rather guarded in our judgment of the two latter groups of cases, for they are not usually seen until compensation has become broken.

The Inefficiencies of a Compensated Circulation.—The hypertrophy which enables the heart to carry on the circulation under pathological conditions is spoken of as a compensatory hypertrophy. This does not mean that the new circulatory mechanism is just as effective as the old. According to the view of Romberg and of the author, however, the power of the hypertrophied heart muscle to accommodate itself to further new demands is equal to that of the intact muscle.[61] An illustration will show what complex factors are involved in the consideration of this problem. Romberg has shown that ani-

[60] See Roy and Adami, Brit. Med. Jour., 1888, vol. ii. p. 321.
[61] Romberg and Hasenfeld, Arch. f. exp Path, vol xxxix. p. 333.

mals with an aortic insufficiency are capable of overcoming increased resistance, produced by compression of the aorta, for as long a time and with as little fatigue as are normal animals. During the earlier period of increased resistance, however, their blood-pressure is not maintained at so high a level, and the more severe the insufficiency the lower is the blood-pressure. Yet this effect cannot be attributed to a diminished power of accommodation in the hypertrophied muscle. The increased resistance, raising the blood-pressure, causes more blood to leak back into the ventricle during diastole, so that the left ventricle has two unfavorable factors to contend with, increased resistance and a greater leak in its valves. The accommodative power of the muscle, therefore, would have to be greater than that of the normal muscle to overcome an equal rise of blood-pressure. If we compare the behavior of a heart sustaining a recent aortic insufficiency where there is no hypertrophy, with one that has had time to hypertrophy, then the greater reserve force of the latter is well shown under the conditions of Romberg's experiment. It seems to us probable, therefore, that the hypertrophied heart muscle possesses the same amount of reserve force as the normal muscle.

And yet, as has been stated, a compensatory enlargement of the heart cannot restore the circulation to a normal condition, and for many reasons. In the first place, the blood-pressure in the pulmonary system must frequently be maintained at a higher level than usual, as happens in many diseases of the left heart and of the lungs (see p. 43). If the high pressure in the pulmonary circulation continues for any length of time, the connective tissue of the lungs increases and small quantities of blood are extravasated. The resulting pigment is taken up by the alveolar epithelial cells, and if these appear in the sputum they are diagnostic of chronic passive congestion of the lungs. These changes in the pulmonary tissues undoubt-

edly interfere with the proper aëration of the blood. The increased pressure in the pulmonary system likewise interferes with breathing. We have no good explanation of the manner in which it does this. Neither the older view that the swollen and tortuous capillaries limit the space in the alveoli, nor the more modern explanation that the lungs become swollen and inelastic,[62] has received general acceptance. The tissues of a lung that is the seat of chronic passive congestion also seem to suffer in nutrition and in resistance to infection. At least, such patients are very susceptible to bronchitis, so that it seems as if the lungs had become less able to resist organisms that may have entered through the upper air-passages. Thus we see that a cardiac lesion, even though compensated, may seriously interfere with the functional capacity of the lungs.

Lesions of the right side of the heart not infrequently lead to stasis in the veins of the general circulation. Since the same condition is produced by any weakness of the right ventricle, it will be considered in that connection.

All patients with continuously high arterial pressure are in danger of rupture of an artery, which is especially true if the walls of the arteries are already weakened. The immediate cause of the hemorrhage is usually some act which itself produces a further rise in pressure, such as excitement, violent exertion, coitus, and straining at stool. In patients with arteriosclerosis or granular kidney, such acts are not infrequently followed by hemorrhages into the brain or retina.

As is well known, the characteristic pulse of aortic insufficiency is one of great excursion. It bounds up against the palpating finger, and as suddenly recedes. It may be transmitted to the capillaries, producing a visible capillary pulse. Such a pulse is not without its effect upon the arterial wall. The rapid and excessive distention may result ultimately in a stretching of the artery, so that vasomotor influences are

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[62] v. Basch, Kongr. f. in. Med., 1889, p. 384.

no longer able to reduce it to its former size. The amount of blood in the body is limited, and, since the dilated arteries contain more blood than normally, there may thus result an inadequate filling of the rest of the vascular system. This is perhaps the explanation of the poor circulation sometimes seen in cases of aortic insufficiency in which there is no weakening of the left ventricle.

Still another effect of an enlarged heart must be mentioned,—viz., the space taken up in the chest cavity and the resultant compression of the other intrathoracic organs.

We have dealt thus far with the heart's condition so long as the body is at rest. If patients with heart disease exercise, the work of the heart is at times enormously increased. We have already described how an increased peripheral resistance affects the work of a heart with an aortic insufficiency, not only by raising the pressure against which it must pump the blood, but by increasing the amount that regurgitates during each diastole (p. 58). Similar relations hold good for other valvular lesions.[68]

Thus we see that, although the hypertrophy of the heart may compensate for the valvular lesion in certain particulars, it cannot restore the circulatory conditions to their normal state.

Myocardial Changes in Hypertrophied Hearts.—And yet the chief source of difficulty with an hypertrophied heart does not lie in any of the factors thus far mentioned, but rather in the condition of the muscle itself. We have taken great pains to show that a healthy hypertrophied muscle possesses capabilities not differing from those of the normal muscle. The hypertrophied heart muscle and the enlarged biceps of the athelete are comparable in some cases, but, unfortunately, it is not so in the majority of instances. For the very causes which lead to hypertrophy of the heart frequently, at the same

[68] Levy, Ztft. f. klin. Med., vol. xxxi. p. 521.

time, produce pathological changes in the myocardium. It will be recalled how frequently the infectious diseases give rise to valvular lesions and consequently to heart hypertrophy. In such infections the myocardium is almost invariably diseased, and often to a greater degree than the endocardium. These diseases, and especially acute articular rheumatism, cause degenerations of the muscle fibres, interstitial myocardial inflammations, and diseases of the arteries.[64] It cannot be doubted that these disturb the functions of the heart muscle most seriously. Such a disturbance may take the form of an acute dilatation, which is not of a compensatory nature, due to the necessity for an increased supply of blood, but which results from the incomplete contractions of the heart muscle. The dilatation of the right ventricle in the early stages of a mitral lesion is usually of this nature. Chronic myocardial changes are likewise of great importance in the subsequent course of a valvular disease. They show a tendency to spread gradually, leaving behind them connective tissue scars instead of healthy muscle-fibres. There is therefore not only a destruction of muscle, but a resulting scar tissue, which undoubtedly hinders the activities of the healthy muscle-fibres that remain.

This is the real cause of weakness in many hearts where valvular disease has been diagnosticated. The myocarditis in such hearts has been frequently demonstrated. It is not necessarily present, it may vary both in location and intensity, and it bears no definite relation to the kind or age of the valvular lesion. It adds an uncertainty to the prognosis of valvular disease, which must always be taken into account. The progressive character of the processes in question is another source of uncertainty. On the one hand, the endocarditis may gradually progress and lead to more and more extensive alterations in the valves; while, on the other hand, the heart muscle may gradually weaken so that it becomes less and less

[64] Albrecht, Der Herzmuskel, II. Teil.

able to respond to the increased calls made upon it. A most unhappy combination!

The weakness of the hypertrophied heart muscle in other conditions is less easily explained. Hypertrophy of the right ventricle often arises from diseases of the lungs. The progressive character of the pulmonary disease may gradually throw an overwhelming burden upon the right ventricle. In other cases, however, no such explanation is possible, and we are entirely ignorant of the reason why the hypertrophied ventricle weakens.

So far as the left ventricle is concerned, the relations are comparatively simple when the hypertrophy arises from an arteriosclerosis, for it is well known that the coronary arteries are frequently involved in this process and that coronary sclerosis leads to most serious disturbances in the nutrition of the heart muscle.

The hypertrophied hearts of patients with nephritis are ofttimes singularly free from signs of weakness. Many patients with granular kidneys maintain a good circulation for years, and only in the last stages of the disease do they develop signs of cardiac weakness. Albrecht[65] has recently shown that, in such cases, disease of the myocardium, sufficient to explain all symptoms, is present.

It is extremely difficult to explain the cardiac weakness that develops as a result of the misuse of beer and wine. In a number of these cases, the extensive fatty degeneration and the fresh inflammatory processes are, however, sufficient to account for all the symptoms.[66] It seems as if such hearts show less resistance to the causes which produce inflammation. The alcohol itself can hardly be the immediate cause of the inflammatory condition, for we know that large quantities of concentrated spirits may be taken without producing any such

[65] Der Herzmuskel, II. Teil.
[66] Krehl, Arch. f. klin. Med., vol. xlviii. p. 414.

changes in the heart muscle. It is, indeed, true that we are unable to positively deny the possibility that alcohol is the sole causative agent in these cases, especially since it is notoriously liable to produce similar changes in other tissues; yet to us it seems more probable that the poison simply prepares the way for the infectious process. No satisfactory explanation can be given of those cases in which there is cardiac weakness without demonstrable signs of disease in the myocardium, and further studies are necessary to throw light on such conditions.

We can now understand how it is that in many instances the hypertrophied heart is less efficient than the normal organ. Hypertrophy itself does not necessarily entail any weakness. Theoretically the hypertrophied organ possesses the same reserve force as the healthy one. Such favorable hypertrophies are, indeed, observed, but unfortunately they are rare. In the majority of cases the cause which induces the hypertrophy also damages the capabilities of the muscle. The heart is so injured that it cannot properly respond to an emergency at the very time when its power to do so is most needed.

For this reason, many hypertrophied hearts are unable to meet any additional call made upon them. They tire much more readily than the normal organ, and when once tired they do not recover so quickly. Indeed, a serious or even irreparable damage may result. On this account, the patient with heart disease is repeatedly warned of the dangers of over-exertion. On this acount, also, women who have heart disease often do badly during a confinement.

Causes of Broken Compensation in Hypertrophied Hearts. —If a heart becomes unable to meet the increased demands that are made upon it, we speak of a break of compensation. This failure in compensation may be brought about in several ways. In the first place, what is ordinarily a moderate call upon the heart may be an excessive one in certain forms of disease. We have already shown, for example (p. 58), that in aortic insuf-

ficiency a rise in peripheral resistance increases the work of the heart, not only by raising the pressure against which it must pump the blood, but by actually increasing the leakage backward into the ventricle during diastole. Even though the accommodative power of the muscle were normal, it might not be able to meet this double demand that is made upon it.

It frequently happens that a break in compensation occurs even though the patient has taken great care not to exert himself. Such a break in compensation may improve, and even be recovered from; but, on the other hand, it may lead to permanent insufficiency or death. The prognosis is decidedly better when the compensation of the right ventricle is alone at fault; and the breaks of compensation which occur in mitral disease are decidedly more favorable than those which develop in a heart in which the left or both ventricles are hypertrophied as a result of continued, severe exertion, arteriosclerosis, or aortic valve disease.

In a certain proportion of the cases in which such a break of compensation occurs, apparently spontaneously, it is to be attributed to a fresh infectious process involving the heart muscle. A second attack of acute articular rheumatism, a pneumonia, or a tonsillitis may in this manner be the immediate cause of a break in compensation. It seems as if the hypertrophied heart muscle formed a *locus minoris resistentiæ* to the infecting organisms or to their toxins.

In another group of cases the apparently spontaneous break in compensation is due to the progressive character of the process that caused the hypertrophy. The demands upon the heart are gradually increased to such an extent that they cannot be carried out. Among such progressive processes are to be reckoned many valvular lesions, pulmonary cirrhosis and emphysema, arteriosclerosis, chronic nephritis, and the excessive use of beer; in a word, they include the majority of all the causes of heart hypertrophy.

Finally, the break may occur, not from any increase in the demands upon the hypertrophied heart, but from a progressive weakening of the muscle through myocardial disease, which renders the heart unable to do even its normal quota of work. This form of cardiac weakness will be more fully considered below.

Causes of Primary Insufficiency of the Heart Muscle.— Some of the causes that lead to a primary weakness of the heart muscle have already been mentioned in the last section. The others may affect either hypertrophied or non-hypertrophied hearts.

Of first importance among these causes are those affections which interfere with the blood-supply to the cardiac muscle, such as thrombosis, embolism, and sclerosis of the coronary arteries. The heart is exceedingly sensitive to changes in its blood-supply. If a large portion of its wall be suddenly deprived of its nourishment, the organ stops beating. This has been observed clinically when an embolus has lodged in a coronary artery, and it has been demonstrated experimentally by ligating one of these vessels. In other cases, where the damage is less extensive, the muscle wall may degenerate and rupture, leading to a fatal hemorrhage within the pericardial sac.

The effect of occlusion of a branch of a coronary artery is variable. In some instances the patient experiences a sensation of oppression or of severe pain in the precordium, which may or may not herald a fatal termination. Porter [57] has shown that it is possible to tie even large coronary branches without causing the death of the animal. Correspondingly, patients have been observed at autopsy who have apparently recovered from extensive infarctions of the heart muscle. There is a slight anastomosis among the branches of the coronary arteries, so that these can no longer be considered end-arteries in the strictest sense of the term. The anastomosis, however, is

[57] Jour. of Phys., vol. xv. p. 122

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insufficient to establish a collateral circulation if an area of any magnitude has been deprived of its regular blood-supply. An area so affected undergoes anæmic necrosis, and in general we may say that the occlusion of a coronary vessel of any magnitude is a matter of most serious import.

Marked general anæmia also injures the heart, either by causing degeneration of its muscle-fibres or by lowering their nutrition in some other, less obvious manner. General bodily malnutrition exercises a similar unfavorable influence upon the strength of the cardiac muscle. It is comparatively unimportant whether the malnutrition arise from poor food, gastro-intestinal disease, or infectious processes. In regard to infectious diseases, however, we must remember that they may injure the heart in a variety of other ways, as by causing myocarditis, or through direct action of their toxins. The symptoms which arise under these circumstances are irregularities of rhythm and, especially, those disturbances referable to a diminution in the heart's capacity for work.[68]

A fresh inflammation of the heart, whether of the endocardium, myocardium, or pericardium, is injurious to the heart's activities. In many cases there is an actual loss of contractile tissue as a result of the inflammation. As we have already mentioned, such changes not infrequently affect hearts which are already hypertrophied. They also occur, however, in previously normal hearts, especially from the general infectious diseases, such as acute articular rheumatism, diphtheria, typhoid fever, and scarlet fever. Such an infectious myocarditis may develop at the height of the disease, or it may not develop until some weeks after the fever has disappeared, as happens especially after scarlet and typhoid fevers.

Numerous poisons may depress the activities of the heart, in some instances after a primary stimulation, as occurs with digitalis and muscarin. It is possible that similar poisons are

[68] Staehelin, Arch. f. klin. Med., vol. lxvii. p. 147.

generated in the metabolism of the body. We know of at least one disease in which the heart changes are probably due to such a cause,—viz., exophthalmic goitre. There is here an increase in the rate and in the force of the heart's contractions. In many cases an hypertrophy of both ventricles develops, and not a few of the patients die with the signs of a cardiac insufficiency. At autopsy hypertrophy and dilatation of the heart are present, but no changes are found in the cardiac muscle.[89] Since the blood-pressure in these cases is not always higher than normal, we must attribute the hypertrophy to the more rapid and forcible heart action, whether produced by nervous or by toxic influences. This illustrates the fact that hypertrophy may develop as a result of increased cardiac activity without there being any rise of blood-pressure. The bearing of such a possibility upon the causation of the hypertrophy associated with nephritis has already been considered (p. 51). Just as such toxic influences may increase the activities of the heart, so may they also lead finally to a weakening of the muscle.

The toxins produced by bacteria may likewise injure the strength of the cardiac muscle. This has been proved beyond question in the case of the diphtheria toxins, and is probably equally true of others.

It is difficult to say to what extent the so-called degenerations of the cardiac muscle injure the activities of the heart. Where the degenerations are very extensive, there can be no doubt that they cause serious disturbances. When, for example, in phosphorus poisoning, the ether extract amounts to twenty-six per cent. of the dried muscle instead of the normal eleven per cent., and when microscopic examination shows that nearly every fibre is filled with fat droplets, a diminished capacity for work is to be expected. We are not yet able, however, to estimate the effect of the slight and of the moderate grades of fatty or of hyaline degeneration. It is cus-

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[*] Hezel, Ztft. f. Nervenheilk., vol. iv. p. 353.

tomary to attribute cardiac weakness to these conditions. Yet we know that the degenerations may be found in apparently strong as well as in weak hearts.[70] Furthermore, it is possible that the cause of the fatty degeneration may itself independently weaken the cardiac muscle. Brown atrophy has hardly any clinical significance, and we are not yet able to say what functional effect is produced by fragmentation of the cardiac muscle.

The so-called fatty heart remains to be considered. This term has been applied to two separate conditions,—fatty degeneration of the muscle-fibres, and excessive fatty infiltration into the interstitial tissue. The two affections have nothing whatever to do with each other, and fatty degeneration rarely occurs to any marked degree in hearts which are the seat of fatty infiltration. The latter are usually associated with a general lipomatosis, and it is to them that the term " fatty heart" is more commonly applied. It is uncertain how much this excessive fat about the muscle-cells injures their functional activity. The muscular tissue is often surprisingly reduced in such hearts, probably from the pressure of the fat; possibly, however, because the atrophy of the muscle is primary, the infiltration of the fat secondary. The disturbances of function in such hearts are probably due to the small amount of cardiac muscle present, relative to the total body weight. In other cases coronary sclerosis or other sequels of overindulgence in wine or beer constitute the cause of the cardiac weakness.

Finally, there is a group of cases exhibiting weakness of the heart to which the term of " functional disturbances" has been applied. Such a term simply means that at present we are ignorant as to the cause of these disturbances. The number of cases included in this group will progressively diminish as our knowledge increases. At the present time we must place in this group many of those cases of hypertrophy in which

[70] Welch, Med. News, 1888.

the demands so increase that the heart is no longer able to meet them, as well as many cases of heart weakness resulting from disturbances of the general nutrition. Many of the so-called nervous derangements must likewise be placed in this group.

Fatigue of the heart is just as little understood as is fatigue of the skeletal muscles. We speak of fatigue when the strength of a muscle diminishes as the result of exercise, and which is recovered after a period of rest. If the heart be diseased, it is fatigued by a smaller amount of work than is the normal organ, and not infrequently it recovers slowly or not at all.

If sudden excessive demands be made upon a normal heart, it usually becomes fatigued, and after a rest it recovers. There have been cases described, however, in which a heart, as the result of a brief but excessive amount of work, was said to have been permanently injured, or, indeed, to have given out entirely. It has been considered that this resulted from an excessive dilatation of the heart. We know that such an acute dilatation with an arrest in diastole may be produced experimentally in animals by greatly increasing the resistance against which the heart must pump. The possibility that a similar result may occur in man from excessive exertion cannot be denied absolutely. Yet the probabilities are entirely against this view.[71] In the reported cases of heart-failure following exertion, too little attention has been paid to the condition of the heart muscle, which has, in most instances, been previously damaged.

There is no doubt that the diseased heart is not only easily fatigued, but that it is especially liable to become overdistended. When a convalescent from typhoid fever or diphtheria drops dead suddenly after some unusual exertion, it is usually from this cause. It is probable that fatigue or acute dilatation of a

[71] de la Camp, Ztft f. klin Med., vol. li. p. 1.

slightly damaged heart frequently occurs without being recognized, and there always exists the danger that too much will be demanded of such a weakened heart.

The influence of the nervous system upon the heart remains to be considered. It is theoretically possible that gross or microscopical lesions of the central nervous system should exercise an unfavorable influence upon the heart's activities because they injure the centres which regulate the heart, yet we have at present no direct evidence to prove that an injurious effect is actually produced by these causes.

The central nervous system does in certain cases influence the heart unfavorably, but it is through the so-called psychic influences, which are of quite a different nature. It is well known that sorrow, worry, and care may affect the heart, not only in its rhythm, but in its strength. This is frequently observed in those suffering from heart disease, but it may occur also in healthy individuals. Indeed, the depression of the heart's activities may be so extreme as to terminate fatally.[72] Neurasthenics frequently suffer from distressing cardiac sensations, from irregularity of the heart's action, and even from cardiac weakness. This last, however, is not common, and it is more frequently a part of a general muscular weakness.

Many are inclined to refer various disturbances of the heart's function to disease of the nervous mechanism situated within the heart itself, but we are without any exact knowledge on this subject.

Cardiac weakness is ordinarily regarded as a weakness in the contractile power of the heart. Yet disturbances in the dilatation of the heart might almost equally well lead to serious consequences,[73] for diastole is not a merely passive process. There is probably an active dilatation at the beginning of diastole, and toward the end there is a rapid increase in the

[72] Bollinger, Münch. med. Wochenschr., 1888, No. 20.
[73] Romberg and Hasenfeld, Arch. f. exp. Path., vol. xxxix. p. 341.

tension of the muscular wall which limits the degree of filling of the ventricle. If these acts are improperly performed, serious alterations in the circulation would result, and possibly the effects of such disturbances will play an important part in the heart pathology of the future. At present, however, we are utterly ignorant of their practical significance.

Results of Cardiac Weakness.—In the consideration of the effect of cardiac weakness upon the circulation, it is immaterial whether the heart is primarily weakened so that it is unable to fulfil the ordinary demands of the circulation, or whether the demands are so increased that they become excessive.

Even the healthy ventricle does not expel the blood completely when increased quantities must be pumped with each contraction. If the auricle weakens, it soon ceases to contract, especially if it be distended. This has been observed experimentally and clinically.[74] If the ventricle be weakened, it does not contract so completely as does the normal one, and a smaller amount of blood than usual is expelled at a lower rate of speed. The aorta is less completely filled and the arterial pressure sinks. The flow of blood into the ventricle is impeded, for not only is there less available space in the ventricle owing to the incomplete expulsion of blood, but the suction of early diastole is also probably weakened. Consequently the entrance of blood into the ventricle is impeded, the veins become distended, and the venous pressure increases.

The effects are best studied in those cases in which both ventricles are equally or nearly equally affected, which is, indeed, the commonest form of cardiac weakness. The insufficiency of the left ventricle lowers the systemic arterial pressure, while the insufficiency of the right ventricle increases the pressure in the systemic veins. The difference in pressure be-

[74] D Gerhardt, Arch f exp. Path., vol. xlvii p. 250; Mackenzie, The Study of the Pulse, etc., 1902, chap. xx.

tween the veins and arteries, therefore, is less than it is normally, and consequently the rate of flow in the capillaries is lessened. At the same time, the distribution of blood is affected, for the arteries contain less, the veins more, blood than normal. Thus the result of a weakening of both ventricles upon the greater circulation is a diminished arterial pressure, an increased venous pressure, a diminution in the rate qf bloodflow, and an overfilling of the veins with blood. Somewhat similar conditions result in the pulmonary circulation.

If only one ventricle be weakened, or, as is more frequently the case, if one be decidedly weaker than the other, then the effects are quite different. Let us first consider the consequences of a weakened left ventricle. This leads to a lower pressure in the systemic arteries, and consequently to a slower rate of flow in the capillaries. The venous pressure in the pulmonary system is increased, and this leads to increased pressure in the pulmonary arteries, which necessitates more work for the right ventricle, as we have already explained (p. 43). Although the flow of blood through the lungs is maintained as well or nearly as well as before, yet the pulmonary vessels are overfilled, and this is not without its effect upon the interchange of gases in the lungs (p. 58). Furthermore, these pulmonary changes react upon the general circulation, for the intrathoracic pressure is increased, and this lessens the aspiration of the blood from the great veins. In this manner an uncomplicated weakness of the left ventricle may cause stasis in the veins of the general circulation. In practice such a stasis is greatly favored by the fact that nearly every case of weakness of the left ventricle is associated with more or less weakness of the right. It may be asked whether or not it is possible for the right ventricle to pump its regular quota of blood if the left is only pumping a part of what it should. Such a condition would ultimately lead to an accumulation of all the blood of the body in the lungs. If life is

to be maintained, a stationary period must develop in which both ventricles pump equal amounts of blood. But during the time that it is developing, there is a gradual accumulation of blood in the lungs, so that in the fully developed condition there is an abnormal distribution of blood, more being in the lungs and less in the general circulation, even though both ventricles are now pumping equal amounts.

If the right ventricle is insufficient, less blood is sent into the pulmonary arteries, the pulmonary pressure falls, and the rate of flow in the lungs is diminished. Less blood is taken from the great veins of the general circulation, these become swollen, and all the organs, especially the liver, become hyperæmic from the venous congestion. The blood-flow in the general circulation is retarded, chiefly because the left ventricle cannot pump more blood than is furnished to it by the weakened right ventricle.

As a matter of fact, cases in which one ventricle alone is weakened are extremely rare. Most injurious agents affect both sides of the heart. Diseases of the lungs, however, affect chiefly the right heart, while arteriosclerosis leads to disease of the left. In these conditions, therefore, we are most likely to see pathological pictures corresponding to those just described as characteristic of weakness of only one ventricle. In all cases the blood-flow is retarded and there is labored breathing on account of the lessened amount of blood which traverses the lung in a unit of time. The disturbances of breathing are greater when the left ventricle is weakened, because this causes in addition a passive congestion of the lungs; whereas when insufficiency of the right heart exists alone, the blood tends to collect in the systemic veins without producing a pulmonary congestion.

Of the harmful effects resulting from cardiac weakness, the most serious is unquestionably the slowing of the blood-current; next to this is the change in blood-pressure. We are

accustomed to regard the latter as the more important, perhaps because estimations of the blood-pressure are made with comparative ease. Yet in the last analysis the rate of blood-flow is of greater importance. This rate is, of course, largely dependent upon the arterial pressure, owing to the narrow range within which the venous pressure varies. (No deductions as to the rate of blood-flow can be made from the systolic arterial pressure alone, for with the same pressure the flow may vary enormously, depending upon the amount of resistance which it encounters in the smaller arterioles. The estimation of the difference between the systolic and diastolic arterial pressure promises to give us a rough method of estimating the flow of blood through the arteries.—ED.) Nor can we say that the higher the arterial pressure the more favorable the condition, for a diminution of arterial pressure under certain conditions is of distinct advantage, and a great increase in pressure brings with it certain dangers. On the other hand, the lowering of pressure must not be excessive, for a certain arterial pressure is absolutely necessary to maintain the rate of blood-flow essential for the proper performance of the functions of the body.

Disturbances of the heart's strength lead to its enlargement through a dilatation of its cavities. The weakened ventricle is unable to empty itself as completely as does the healthy one, and a certain amount of blood is left in it at the end of each systole. In diastole, likewise, it contains more blood than normal. There is, therefore, a dilatation of the ventricular cavity, and physical examination demonstrates an enlargement of the area of cardiac dulness. This dilatation of stasis must be sharply distinguished from the compensatory dilatation which we have already described in connection with certain valvular lesions. The latter are hardly pathological, for they are necessary in the accommodation of the heart to the new circulatory conditions. Only by such a compensatory

dilatation is the heart enabled to maintain a proper circulation in such valvular affections as aortic insufficiency (see p. 34). The dilatation which we are here considering is *not* of a compensatory nature, and it occurs only when the heart is unable to do its work. Although the normal heart does not empty itself completely when very large amounts of blood must be propelled, yet it soon regains its usual condition after the unusual demands have passed. In a case of pathological dilatation, however, a complete systole never occurs, and the heart's cavities are constantly overfilled.

This dilatation of a weakened heart may arise from many causes. A heart may be unable to maintain the circulation even when the body is at rest, in which case it is in a state of continual dilatation. On the other hand, the insufficiency may only develop when some extraordinary demands are made upon the heart, and in this case the dilatation is temporary. Hypertrophied hearts are especially susceptible to dilatation. They may maintain the circulation for years, in spite of the extra work necessary, but finally injurious influences weaken the muscle, or the work to be performed gradually increases beyond the capacity of the heart, and then dilatation follows. Frequently hypertrophy and dilatation develop together. This occurs when, at the same time, increased work is necessary and injurious influences act on the cardiac muscle. The ultimate outcome of such a case depends upon the relation between these two factors. If the hypertrophy be in excess, the prognosis is comparatively good, whereas if the dilatation be in excess it is comparatively bad. A dilated heart may gradually strengthen and hypertrophy, so that it will accommodate itself to the increased amount of work necessary.

One effect of the poor circulation is a deficient supply of oxygen to, and an imperfect removal of carbon dioxide from, the tissues. The lessened blood-flow in the lungs also diminishes the interchange of gases there. The patient feels

that he needs more air. The lack of oxygen and especially the presence of carbonic acid gas in the blood stimulate certain cells of the medulla oblongata, and this stimulation causes more frequent and deeper respirations. (See Dyspnœa, in the chapter on Respiration.) The increase in respiratory movements may partly compensate for the slower blood-flow, but it does not do so wholly.

The stasis of blood in the veins of the general circulation is very apparent. The superficial veins are enlarged and tortuous, and many, not before visible, appear. The poorly aërated blood gives a bluish tinge to the skin, which is usually most marked in the nose, ears, cheeks, fingers, and toes, probably on account of relative coolness of these parts.

The highest grade of cyanosis without a correspondingly great cardiac insufficiency is seen in congenital defects of the right heart. The fingers acquire a characteristic club-shape, owing to changes in the bones, and these, with the broad, dark-blue finger-nails, present a very characteristic appearance. It is difficult to give an adequate explanation of this cyanosis of congenital heart disease. A number of factors probably combine to bring it about. In the first place, owing to the inability of the right ventricle to completely compensate for the defect, there results an insufficient aëration of the blood and a stasis, the latter being evident from the tortuosity of the veins of the skin and of the backgrounds of the eyes. In the second place, a defect in the ventricular septum, so commonly associated with congenital lesions, allows the arterial and the venous blood to mix. Finally, the well-known increase in the number of red blood-corpuscles in a unit-volume is probably an important factor, which may account for certain cases of cyanosis that cannot be explained in any other manner.

The venous hyperæmia causes a swelling of distensible organs. The kidneys become enlarged and dark blue, and their secretion is altered in a characteristic manner. The liver

becomes swollen, hard, and tense, producing a distressing feeling of pressure in the abdomen, or, indeed, actual pain. The plasma escapes from the capillaries into the subcutaneous tissues, causing œdema. Transudation into the serous cavities may also take place.

If the veins are much swollen, they frequently pulsate synchronously with the heart-beats. These pulsations are most marked in the jugulars, but they may be present in the veins of the upper extremity or of the chest wall.[75] They are due, in the first place, to an insufficiency of the valves of the affected veins, which allows the pulsations normally present in the superior vena cava to be conducted to the peripheral veins. Such a "normal," "negative," venous pulse arises from a hinderance to the venous flow of blood caused by each contraction of the right auricle. The vein is most distended during auricular systole just before the contraction of the ventricle. Tricuspid insufficiency produces a venous pulse of a totally different character. Here the vein is distended by the blood which regurgitates from the right ventricle through an insufficient tricuspid valve, and the greatest distention occurs synchronously with or just after the ventricular systole. This is called a "pathological," "positive" venous pulsation. Without the aid of accurate tracings[76] it is often extremely difficult to determine which form of pulsation is present, owing to the irregular heart action and to the dyspnœa.

Disturbances of the Heart-Rate.—Disturbances of the rate of the heart's beat may be due to a weakening of the heart or may be independent of such weakening. The heart-rate varies greatly even in health. It usually becomes slower with age, although in extreme old age it may again become more rapid. It is interesting to note that at this age the vagus tone is slight

[75] D Gerhardt, Arch. f. exp. Path , vol. xxxiv. p 402; Mackenzie, The Study of the Pulse, etc

[76] See Mackenzie, loc cit.

or may be completely absent.[77] There are great individual variations in the heart-rate: while some have a normal rate of fifty-six to sixty-eight per minute, others have a pulse-rate of seventy to eighty. As a rule, the rate is more rapid in women than in men. It is not our intention to name all those influences which affect the rate of a normal heart. The mode of action of many is easily understood, whereas others have not yet been explained.

Physiological studies [78] have demonstrated that the contraction of the heart is initiated by a periodic stimulation of the fibres situated at the entrance of the great veins into the auricles. This stimulation is propagated from there over the whole heart, and causes its parts to contract in a regular sequence. The rhythm of a normal heart may seem absolutely regular to an ordinary observer, but more exact methods have shown that there are distinct physiological differences in the duration of the pulse-waves. According to Englemann, the heart's action may be affected in various ways. There may be variations not only in the regular sequence of the stimuli (chronotropy), but in the ability of the heart to respond to these stimuli (balmotropy). Furthermore, the propagation of the stimuli over the heart (dromotropy), as well as the contractility of the muscle (inotropy), may be abnormally increased or diminished. The causes of disturbances of cardiac rate and rhythm may lie either in the muscle itself or in its nervous connections.[79] Thus we see how complicated are the conditions governing the rate and rhythm of the heart, and how difficult it must be to interpret the many clinical variations.

Rapid Heart Action (Tachycardia).—In certain conditions the cause of an abnormally rapid heart action is clear. For

[77] Dehio, Arch. f. klin. Med., vol. xli. p. 74.

[78] Gaskell, Jour. of Phys., vol. iv. p. 44; Engelmann, Pflüger's Arch., vol. lxv. p. 535.

[79] Engelmann, Pflüger's Arch. vol. lxv. pp. 109, 535.

example, atropine and similar drugs frequently increase the heart-rate by paralyzing the terminations of the pneumogastric nerve, although they can do this only in individuals in whom the vagus normally exerts an inhibitory action upon the heart. The same effect may be produced by pathological conditions of the vagus fibres or nuclei. Thus the rapid heart action which is so frequently observed at the end of meningeal inflammations is due to a vagus paralysis following the period of vagus stimulation. Not infrequently a pulse-rate of 100 to 160 is observed in such cases without there being any other cardiovascular symptoms.

It is more difficult to explain the rapid heart action due to exertion which is so frequently seen in convalescents, anæmic individuals, and in those who have heart disease. It is possible that there is here an increased irritability either of the heart itself or of its nervous connections, so that the chemical products of muscular activity produce an unusual effect upon one or other of these tissues.

Fever also causes a rapid heart action, for the increased temperature of the body stimulates both the central endings of the accelerator nerves and the heart muscle itself. If no other disturbing factors come into play, the rate of the heart increases proportionately to the rise in temperature. This parallelism between the temperature and the heart-rate is missed in certain infections. For example, in typhoid fever the pulse is relatively slow. With a temperature of 104° F. (40° C.), we may have a pulse of seventy or eighty. In scarlet fever, on the other hand, the pulse-rate is usually surprisingly rapid. In these diseases the action of toxins probably modifies the usual relation between the temperature and the pulse-rate.

A diminution in the arterial pressure is usually accompanied by an acceleration of the pulse. In many cases this is to be explained by the fact that there is a fall in cerebral

pressure, which stimulates the central endings of the accelerator nerves. The purest example of this accelerating action is seen in the rapid pulse of widespread vasomotor paralysis (see p. 112). We frequently observe a rapid pulse in cases of cardiac weakness also, but in such cases it is uncertain whether the rapid heart action is attributable to the heart disease itself or to the fall in pressure. Experiments on animals would seem to indicate that an uncomplicated cardiac weakness leads to less frequent contractions, a fact favoring the hypothesis that the rapid action of the weakened heart is really due to the stimulation of the accelerator fibres occasioned by the lowering of the blood-pressure.

In exophthalmic goitre the tachycardia may be continuous or it may occur in paroxysms. The symptoms of this disease are now attributed by many to an excessive thyroid metabolism, and it seems probable that the cardiac disturbances are likewise due to this cause (see Chapter VII.). Heart symptoms of like nature may also develop in other diseases of the thyroid gland.[80] We are ignorant as to which part of the cardiac mechanism is affected in these cases, whether it be the muscle, the cardiac ganglia, or the central nervous connections.

The tachycardia of nervous people resembles that occurring in exophthalmic goitre. Even in healthy individuals an increased heart-rate may be induced by various influences, as exercise, psychic disturbances, and indigestion; but in nervous people the response to these influences is excessive. It is possible that the seat of the increased irritability is located in the cardiac muscle, for similar variations in rate are seen in those who suffer from disease of the myocardium, and in them at least there is no reason to assume that the condition is in any way dependent upon disturbances of the nervous system.

A rapid heart-rate may be produced by disease of various other organs of the body, such as the peripheral nerves (espe-

[80] Minnich, Das Kropfherz, Leipzig, 1904.

cially of the left arm), the lungs, the liver, the genitals, and the gastro-intestinal canal. When the primary disease is cured, the cardiac disturbances disappear. Apparently such disturbances are due to reflexes from the diseased organs, a view which is supported by many facts. The patients are usually neurotic, the disturbances come and go in perplexing succession, and they furthermore usually arise from organs that are innervated by the vagus nerve. So far as the gastro-intestinal canal is concerned, the absorption of toxins might be the cause of the cardiac disturbances, but this explanation will not hold for the cardiac symptoms arising from disease in other organs.

The condition known as paroxysmal tachycardia [81] is characterized by an enormously accelerated heart-rate, which begins suddenly, lasts a short time, and ceases as suddenly as it began. It may affect individuals with apparently normal hearts, or it may occur in those suffering from some definite cardiac disease. The duration of the attack may be minutes, hours, days, or even weeks. The pulse-rate usually ranges between 150 and 300 per minute. The heart rhythm is regular and the sounds clear. The difference between the quality of the first and that of the second sounds tends to disappear, a common phenomenon in any great acceleration of the cardiac rate. The pulse is small. Ofttimes it cannot be counted. The blood-pressure is usually low, probably because the shortness of diastole does not allow time for a complete filling of the ventricle. The patient may or may not suffer from dyspnœa. The jugular veins are always swollen and usually pulsating. Other signs of venous stasis, such as swelling of the liver, albuminuria, and even œdema, may develop.

Very often, even at the beginning of an attack, the heart is found to be enlarged, a noteworthy fact. Immediately after the attack it returns to its former size. Nevertheless, we have no right to consider this dilatation as the cause of

[81] A. Hoffman, Arch. f. klin. Med., vol. lxxviii. p. 39.

the paroxysm, for it has been found absent in some cases, by the most careful observers.

An acute distention of the lungs has also been noted in certain cases, and the respiratory movements of the edges of the lungs have been diminished. To what extent these changes affect the heart is not definitely known.

Subjective symptoms are always present. During the paroxysm nearly all patients feel weak and faint, most of them suffer from dyspnœa, and some experience the sense of impending death. As a rule, the symptoms begin and end suddenly, frequently with peculiar sensations in the precordium; yet in some cases it is almost certain that the paroxysm may begin or end gradually.

During the intervals between attacks the heart is often normal, so far as can be determined by physical examination. We should, however, be very cautious in our judgment of such cases, for it is difficult to exclude a coronary sclerosis, and many sufferers from this form of tachycardia are the subjects of easily recognized heart lesions.

The individual attack may begin spontaneously, or it may be precipitated by some unusual exertion, by excitement, or by gastro-intestinal disturbances. These same causes normally lead to an acceleration of the heart's action, and it may be somewhat difficult to determine in the individual case whether the attack is really one of paroxysmal tachycardia or not.

We are at present quite ignorant of the essential nature of this disease. It is impossible to produce such paroxysms of tachycardia, either in animals by vagus inhibition or in man by the administration of atropine; yet many facts would seem to indicate that the disease is really of nervous origin,[82] chief among them the fact that, in many patients, pressure upon the vagus nerve will abort a paroxysm.

(Hoffmann has made the important observation that the

[82] Rose, Berl. klin. Wochens., 1901, pp. 713, 744.

pulse-rate during the attack of paroxysmal tachycardia is precisely double that immediately preceding or following the attack,[83] and some of Mackenzie's tracings support the same view.[84] These observations have given rise to the interesting hypothesis that normally the heart receives a greater number of stimuli than are responded to, and that the condition in paroxysmal tachycardia is merely one of an increased responsiveness to these additional normal stimuli.—ED.)

The effect of an acceleration of the heart-rate upon the circulation is variable. It may lead in the first place to an increased blood-flow; but, on the other hand, the shortening of diastole may cause an insufficient filling of the ventricles with consequent retardation of the circulation. Thus experimental stimulation of the accelerator nerve produces more rapid and powerful cardiac contractions and an improvement of the circulation, whereas even the moderate acceleration caused by a vagus paralysis may lead to a slowing of the blood-current.[85] A tachycardia may therefore affect the circulation of a patient in various ways, and numerous other factors must be considered in the individual case.

Slow Heart Action (Bradycardia).—A slow heart-rate may be due, in the first place, to a stimulation of the vagus nerve. We have an example of such a stimulation in the slow pulse of asphyxia. The venous blood stimulates the central endings of the pneumogastric nerve most powerfully. This tends in a certain degree to counteract the great rise in blood-pressure produced by the simultaneous constriction of the splanchnic vessels.

The central terminations of the vagus nerve are likewise stimulated by any rise in the general arterial pressure. Slowing of the pulse is therefore always produced by such a rise,

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[83] Hoffmann, loc. cit., and Ztft. f. klin. Med., vol. liii. p. 206.
[84] Mackenzie, The Study of the Pulse, etc., Figs. 91 and 107.
[85] v. Basch, Phys. u. Path. d. Kreislaufes.

unless other opposing factors are simultaneously operative. For example, the high blood-pressure due to acute nephritis nearly always causes a slowing of the pulse, and the slow pulse of digitalis is due in part to the same cause. If, however, the pressure rises gradually, and if it remains high for a long time, as happens in chronic nephritis and in some cases of arteriosclerosis, then there is usually no reduction of the pulse-rate. The vagus endings probably become accustomed to the changed conditions, so that they no longer respond to the high arterial pressure.

A rise in cerebral pressure will likewise stimulate the vagus, and we always find a slow pulse in those conditions which lead to rapid increase of pressure in the cranial cavity, such as intracranial hemorrhages and extensive meningitis. In such cases the vagus pulse is of great diagnostic significance.

The vagus may be stimulated reflexly. The slow pulse observed at the onset of vomiting is caused by such a stimulation of the pneumogastric nerve, the blood-pressure being lowered at this time. This stimulation is usually due to a reflex from the stomach, although the vagus centre may be directly affected, as happens in the vomiting from increased cerebral pressure or from the action of such drugs as apomorphine. Clinically a reflex vagus pulse is frequently seen in the acute dyspepsia of children, in peritonitis, in strangulation of the intestines, and in chronic constipation. In such conditions the stimulation may produce not only a slow, but an irregular heart action.

Bradycardia may be produced by the direct action of certain poisons, as, for example, muscarin and the bile salts.[86] In the early stages of catarrhal jaundice, there is always a slowing of the heart-rate, and often irregularities of rhythm. In the chronic jaundice accompanying diseases of the liver itself, and in those associated with infectious diseases, the bradycardia is

* Weintraud, Arch. f. exp. Path., vol. xxxiv. p. 37; Brandenburg, Berl. klin. Wochensch., 1903, No. 38; Suppl., p. 149.

often absent, probably because smaller amounts of bile salts are manufactured or because other factors influence the heart. Even in the marked jaundice of chronic obstruction of the common duct by stone or by tumor there is frequently no slowing of the pulse. This is probably due to a diminished production of the bile salts, although possibly the body becomes accustomed to their presence. Experimental investigations have shown that the bile salts act both upon the central and the peripheral terminations of the vagus nerve, as well as upon the cardiac muscle itself. In catarrhal icterus, we cannot say at present which action is the most important in the production of the typical slow pulse. The hypothetical uræmic poison likewise slows the heart-rate, but we are ignorant of the manner in which it acts.

In all cases of continued vagus irritation the slowing of the pulse is only of moderate grade, rarely going below 44 to 48 per minute. The irregular pulse so frequently observed in these conditions well corresponds with the results of experimental stimulation of the vagus nerve.

All varieties of bradycardia, other than those caused by vagus stimulation, are difficult to explain. A slow pulse may be present in neurotic individuals, but we are unable to say whether the immediate cause lies in some alteration in the nervous system, or in some changes in the heart muscle.

There is a group of bradycardias caused by changes in the heart itself. An increase in intracardiac pressure will cause a slowing of the heart-rate, as may be observed in cases of aortic stenosis and also, in certain instances, as a result of unusual, excessive exertion. In such cases the bradycardia is advantageous, for it tends to lessen the work of the heart.

The bradycardias which follow infectious diseases are likewise due to changes in the heart. They may be likened to the subnormal temperature which is so frequently present under like conditions. The slowing of the pulse is most marked after

pneumonia and typhoid fever. The injection of atropine does not affect the bradycardias of this origin.[87] Since atropine paralyzes the vagus terminals, and since the paralysis of these terminals does not affect the bradycardias under consideration, it must be inferred that they are due to changes in the cardiac muscle. Many would attribute this slowing of the heart to fatigue of the muscle. Yet we know that fatigue is not usually associated with a slow pulse. Furthermore, it has not been shown that all infectious diseases necessitate increased work for the heart, which is especially true of typhoid fever with its relatively slow heart-rate. It seems more probable, therefore, that the post-febrile bradycardia is really an expression of cardiac weakness. This is not synonymous with fatigue, for the latter presupposes a previous period of exertion. We know that the weakened heart not infrequently contracts at a slower rate than normal. We also know that other signs of weakness are frequently present during convalescence, and that a cardiac insufficiency is especially prone to develop at this time.

The bradycardias which appear at the height of infectious diseases, especially that ominous slowing of the pulse during the course of diphtheria, are doubtless to be referred to changes in the cardiac muscle itself. Before they can be accurately classified, however, it will be necessary to determine their exact relation to the various degenerations in the heart muscle which occur in these diseases.

Anatomical changes in the myocardium may lead to a slowing of the pulse. This is seen in both acute and chronic myocarditis, as well as in the changes which follow diseases of the coronary arteries. The pulse may fall to twelve a minute in these conditions, and a slow pulse may persist for years. A slow pulse is furthermore observed occasionally in very stout individuals, and in those who have devoted themselves over-zealously to the pleasures of the table, of wine, and of tobacco.

[87] Dehio, Arch. f. klin. Med., vol. lii. p. 74.

We are inclined to attribute the bradycardia in such individuals to an associated coronary disease.

Observations on the venous pulse have demonstrated that in certain cases of slow arterial pulse the auricles are contracting more rapidly than are the ventricles. This is seen most frequently in that paroxysmal type of bradycardia known as the Adams-Stokes disease.[88] To explain the difference in rate between the ventricles and the auricles, we may assume that some of the waves of contraction, which normally proceed from the auricles to the ventricles, are blocked at the auriculo-ventricular (ring) so that the ventricles contract less frequently than do the auricles, thus giving rise to the so-called blocked heart.

The bradycardia of the puerperium is probably due to the decrease in the work of the heart which follows the delivery of the child.

We have already mentioned some of the effects of a slow heart action upon the circulation. The heart is enabled to recover itself during the lengthened diastolic pause, and its work is, to a certain extent, diminished. The velocity of the blood-current is lessened, yet this may be very slight if the slowing of the heart is only moderate in degree. If the brady-cardia be due to vagus irritation, the individual contractions are not only less frequent but they are less forcible, and the current may be slowed considerably. Whenever the brady-cardia is extreme, the velocity of the blood-stream and the arterial pressure are always markedly diminished. Such patients cannot exert themselves without dyspnœa, and even when at rest they may suffer from syncopal attacks.

Disturbances of Cardiac Rhythm (Arrhythmia).—Our knowledge of the disturbances of the rhythm of the heart is naturally limited by our knowledge of the origin and nature of

[88] His, Arch. f. klin Med , vol. lxiv p 316; Osler, Lancet, August 22, 1903

the normal cardiac rhythm (see p. 78).[89] The pulse is not an absolute guide to the rhythm of the heart; first, because a very weak contraction of the heart may not give rise to an arterial pulse; and secondly, because waves of different size may be propagated at different rates of speed toward the periphery. Thus the rhythm at the wrist may differ considerably from that at the heart.

Forms of Arrhythmia.—(Physiological studies have shown that the heart may be made to contract prematurely if an "extra stimulus" be applied, either to a ventricle or to an

FIG. 1.
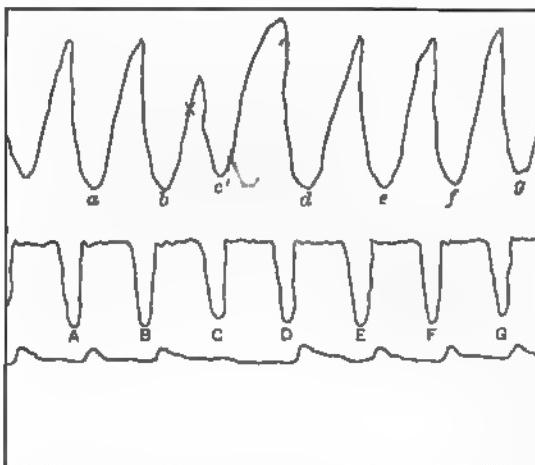
The upper tracing was drawn by the ventricle, the middle by the auricle, and the lower by a sphygmograph attached to the carotid artery. During the systoles of the ventricles and auricles the levers made downward strokes, during diastoles upward strokes. The ventricle was stimulated at x. (From Cushny, Jour. of Exp. Med., vol. iv. p. 329.)

auricle. Such a contraction is called an extrasystole. Thus in Fig. 1, in which the upper tracing represents the contractions of the ventricle, the middle those of the auricle, and the lower the pulse, the ventricle received an electrical stimulus at the point x. It will be seen that this resulted in the premature

[89] Engelmann, Pflüger's Arch., vol. lxii. p. 543; Hering, Pflüger's Arch., vol. lxxxii. p. 1; Ebstein, Arch. f. klin. Med., vol. lxv. p. 81; J. Mackenzie, The Study of the Pulse, etc.

ventricular extrasystole, c', whereas the auricular rhythm remained regular. The stimulus proceeding from the auricular contraction, C, found the ventricle in the refractory period just following its extrasystole c', and consequently it was without effect and this contraction was omitted. The ventricle did not again contract until the stimulus from the auricular contraction D reached it, causing the ventricular contraction d. Since the auricle had maintained its regular rhythm during the extra ventricular contraction, the premature extrasystole, c', is followed by a correspondingly long pause, and the time from b to d is exactly twice that between normal beats. If, as in Fig 2,

FIG. 2.
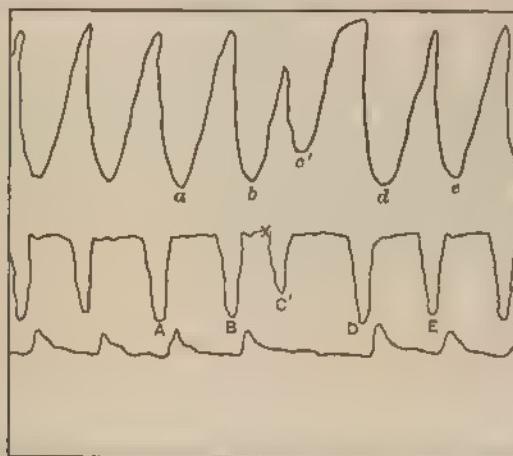
The upper tracing was drawn by the ventricle, the middle by the auricle, and the lower by a sphygmograph attached to the carotid artery. During the systoles of the ventricles and auricles the levers made downward strokes, during diastoles upward strokes. The auricle was stimulated at about the point x. (From Cushny, loc. cit.)

the extra stimulus be applied to the auricle, it is followed by an extra contraction, not only of the auricle C′, but of the ventricle c'. In this instance the auricular rhythm is disturbed, and although there is a compensatory pause after the extra auricular systole, it is not usually long enough to make the total b to d equal to twice the interval between normal beats.—ED.)

The occurrence of extrasystoles in man seems to be favored by a high arterial pressure and by myocardial disease. The premature contraction may occur at varying periods after the normal contraction. The resulting extra pulse is weaker than the normal one, partly because the shortness of the preceding diastole does not allow sufficient time for the ventricle to become completely filled with blood, and partly because the extra stimulus affects the ventricle while it is still in a somewhat refractory stage just following the normal contraction. It is, therefore, a general rule that the earlier the extrasystole occurs after the normal contraction, the smaller will be the resulting pulse. Indeed, the extrasystole may not produce a pulse at all, in which case there is an intermission in the regular pulse rhythm. (See Fig. 1.)

The extrasystole is almost invariably followed by a compensatory pause, owing to the omission of the regular contrac-

FIG. 3.
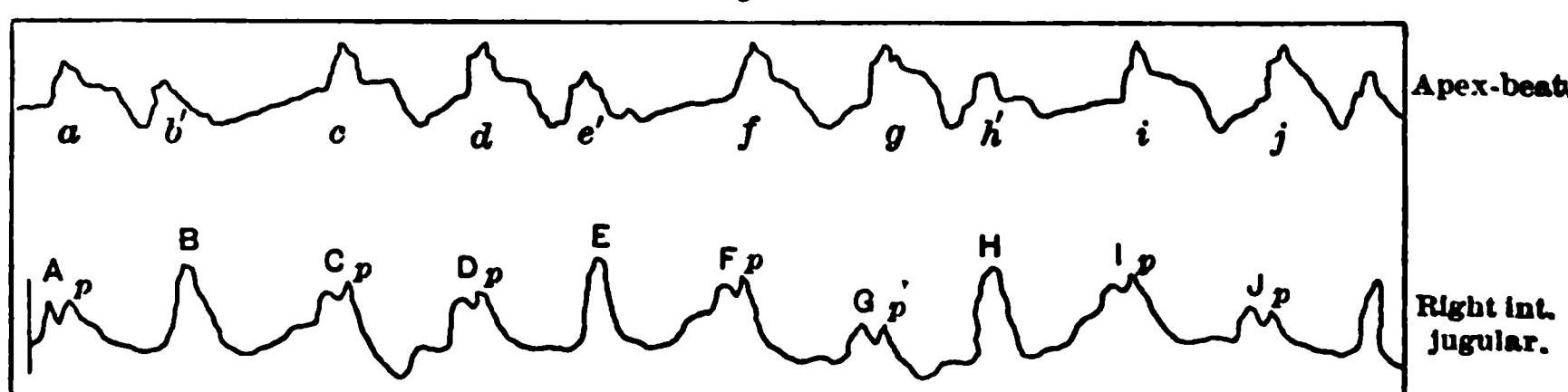
Simultaneous tracings of the apex-beat (contractions of the left ventricle) and of the jugular pulse (contractions of the right auricle). The indentations, marked *p* on the latter, are due to the transmitted carotid pulse. It will be noticed that whereas the auricle contracts regularly, the rhythm of the ventricle is interrupted by a number of extrasystoles, *b'*, *e'*, *h'*, etc., and the interval between the normal contractions preceding and following such extrasystoles, as *d* to *f*, is approximately double that between normal beats, as *f* to *g*. (From Mackenzie.)

tion, that was due immediately after the extra contraction. The time, therefore, between the normal beats preceding and following the extrasystole is approximately twice the normal period between regular beats. We have taken pains to show that when the extra stimulus is experimentally applied to the ventricle, this doubling of the time between normal beats is

very exact owing to the unimpaired rhythm of the auricles. It has also been shown clinically that the auricles do not necessarily participate in the irregular action of the ventricles (see Fig. 3). If the extra stimulus affects the auricles, then they participate in the irregularities of the ventricles (see Fig. 4). In such a case the interval between the normal beats preceding and following the extrasystole may equal two normal intervals, or it may be less than this. If the stimulus be applied to the mouths of the great veins, then the interval is always less than two normal intervals.

Those extrasystoles which are caused by increased arterial pressure usually involve the ventricles alone, whereas those due to myocardial disease may begin either in the auricles or ventricles.

FIG. 4.
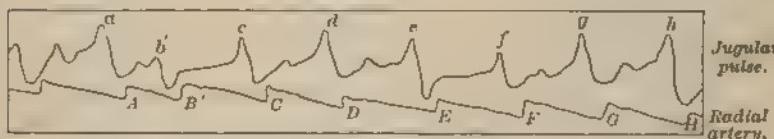
Simultaneous tracings of the radial artery (contractions of the left ventricle) and of the right jugular vein (contractions of the right auricle). It will be noticed (1) that the auricle here partakes in the irregularity, b', and (2) that the interval between A and C is less than twice that between C and D. (From Mackenzie)

(Extrasystoles occur singly or in various combinations. Thus a normal beat may be regularly followed by an extrasystole, producing the well-known bigeminal rhythm. (See Fig. 5.) On the other hand, the extra contraction may follow every second, or every third beat, etc., or a series of extrasystoles may follow one another. In this manner various forms of arrhythmia may be produced by the occurrence of extrasystoles alone.—ED.)

Arrhythmias may be due not to extrasystoles, but to disturbances in the normal automatic stimuli to the auricles. These have been termed "true arrhythmias."[90] The subject

[90] Wenckebach, Ztft. f. klin. Med., vol. xxxvi. p. 181; vol. xxxvii. p. 475; vol. xxxix p. 293.

is, however, still so new that it is hardly permissible for us to draw important diagnostic and prognostic conclusions from the character of the arrhythmia.

FIG. 5.
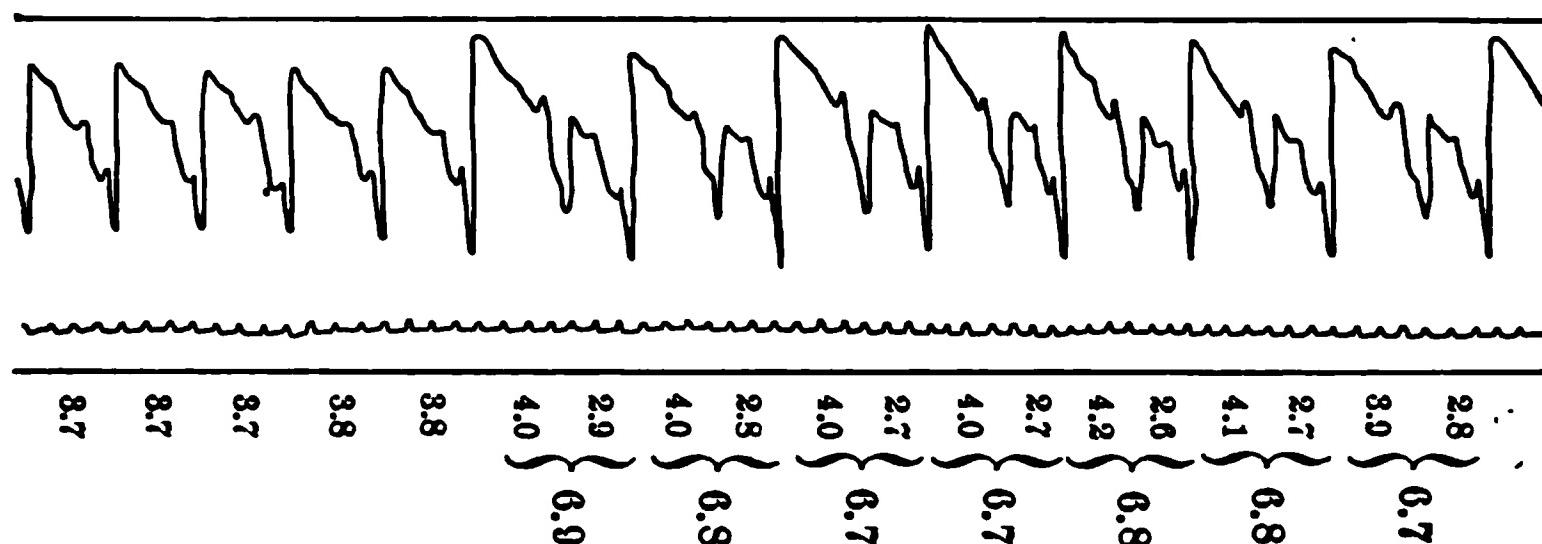
A pulsus bigeminus with the transition to a regular pulse. Notice that the double interval of the former (6.8 fifths of a second) is less than twice the period of a single interval of the latter ($2 \times 3.75 = 7.5$), from which fact we may infer that the extrasystoles were probably of auricular origin.

In those cases in which only every other systole gives rise to an arterial pulse, the possibility exists that the condition is caused by a " hemisystole;" *i.e.*, by the alternate independent contractions of the right and left ventricles. Although this condition of hemisystole has been observed experimentally, we have no proof that it actually occurs in man. Indeed, most of the cases which have been carefully investigated have been shown to be instances of bigeminal rhythm, due to extrasystoles in which only every other contraction gives rise to an arterial pulse.[91] (Some of Mackenzie's tracings (Chapter XXIX.) from dying hearts admit of hardly any other interpretation than that of a non-simultaneous contraction of the two ventricles.—ED.)

The injured heart of an animal may beat at regular intervals, but with alternating strong and weak contractions. Such a " pulsus alternans" is very uncommon clinically, and some claim, indeed, that all cases so reported are in reality instances of bigeminal rhythm due to the occurrence of regular extra-

[91] Riegel, Deut. med. Wochens., 1903, No. 44; Hering, ibid., No. 22.

systoles, although others maintain that a true "pulsus alternans" may occur in man.[92]

Causes of Arrhythmia.—Disturbances of the cardiac rhythm frequently result from disease of the myocardium. Inflammatory processes and infarcts resulting from coronary disease are more frequently the causes of such arrhythmias than are the parenchymatous degenerations of the muscle. A diminished supply of blood to the heart, due to a narrowing of the coronary arteries, may also lead to irregularity. Myocarditis and coronary sclerosis are therefore to be regarded as the most frequent causes of cardiac arrhythmia, and they are doubtless responsible for many of those disturbances of rhythm which occur in the aged. Yet there seems to be no strict relation between the extent of the disease and the degree of irregularity. Possibly the location of the disease is of paramount importance, and it is, indeed, claimed that disease of the auricular musculature is especially liable to lead to irregularities in rhythm. The musculature at the mouths of the great veins, where the contraction wave starts, should be especially examined in all cases of irregular heart action.

Cardiac arrhythmia may occur without any demonstrable anatomical changes in the myocardium. The irregular pulse, which so frequently develops at the height of or during the convalescence from the acute infectious diseases, is probably due to a weakness of the heart, and, as has been mentioned, it is often associated with a bradycardia (p. 85). In many instances this irregularity is only an exaggeration of the slight variations in rate which normally accompany respiration.[93]

An irregular pulse may result from vagus stimulation, for such a stimulation not only slows the heart-rate, but often produces irregularities in rhythm. These irregularities dis-

[92] Hoffman, loc. cit.
[93] Lommel, Arch. f. klin. Med., vol. lxxii. p. 465.

appear if the influence of the vagus upon the heart be eliminated by the administration of atropine.

We are quite ignorant as to the nature of the arrhythmia which is observed in the so-called cardiac neuroses, resulting from neurasthenia, masturbation, excitement, etc. In such cases, the heart may beat first slowly, then rapidly, the individual beats may follow each other quite irregularly, or finally the normal respiratory variations may be excessively exaggerated.[94]

Reflexes may give rise to irregularities of the heart's action. We know that if the endocardium be touched during the course of an experiment, irregularity results. How important a part such reflexes play in clinical pathology is uncertain. Possibly the arrhythmia of endocarditis may arise from such reflexes; possibly the arrhythmias sometimes seen in gastro-intestinal diseases are also of reflex nature. In both these examples, however, there are usually other factors present which might produce an irregular heart action.

Arrhythmia may be due to the action of poisons, notably of digitalis, caffeine, tobacco, and the toxins of uræmia. The irregular tobacco heart is well known. The toxins of infectious diseases, especially those of typhoid fever and diphtheria, may produce similar effects.

In chronic pericarditis and mediastinitis it is possible for the new-formed connective tissue to compress the aorta or the great veins during inspiration. This would lead to a diminution or disappearance of the pulse during inspiration (pulsus paradoxus). Not every pulsus paradoxus is capable of being explained in this manner. It has been observed in simple insufficiency of the heart, and especially in association with stenosis of the larger air-passages, and under such circumstances the cause must lie in the heart itself.[95]

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[94] Lommel, Arch. f. klin. Med., vol. lxxii. p. 465.
[95] Riegel, Deut. med. Wochens., 1903, No. 20.

The Cardiac Impulse.—If we inspect the chest of a normal individual, a periodic heaving is usually seen in the fifth intercostal space, median to the mammary line. This is called the cardiac impulse. It is produced normally by the apex of the left ventricle, which is thrust into the intercostal space with each systole. During diastole, the heart is flaccid and tends to assume the shape given to it by its surroundings, but in systole it becomes rigid and assumes its own characteristic shape. This throws the apex against the chest wall, and is the principal factor in producing the impulse. The main part of the impulse occurs during the first period of systole at a time when all the valves are closed. The heave, however, continues a short time after the opening of the aortic semilunar valves.

Many factors may therefore affect the cardiac impulse, such as the position of the apex within the chest cavity, the force with which the heart contracts, and the condition of the chest wall and the overlying border of the left lung. Provided the latter do not play too great a part, we may say in general that a powerful systole will produce a strong, heaving impulse, and a weak systole will give rise to a small and soft impulse. It cannot be assumed, however, that an extensive, strong impulse is always due to a more powerful contraction of the heart muscle. If an hypertrophy of the right ventricle is mainly responsible for the condition of cardiac hypertrophy, as frequently happens in mitral stenosis, then the apex of the heart is usually formed by the right ventricle.

Long-continued hypertrophy of the heart may lead to a bulging of the chest wall, which is most marked if the enlargement of the heart occurred at a time when the bones of the thorax were soft, and consequently it is most often seen in young individuals.

Attempts to draw deductions from the shape of the graphic representations of the cardiac impulse have proved of little

clinical value. (Mackenzie [96] claims that if the apex of the heart is formed by the right ventricle, there is a systolic retraction in the apical region instead of the normal impulse. It is certain also that tracings of the cardiac impulse may show ventricular contractions which do not influence the radial pulse.—ED.)

The Heart-Sounds.—The heart-sounds may be altered in either their intensity or their character. One of the most important of these alterations is the increase in the loudness of either the pulmonic or the aortic second sound. This accentuation is generally indicative of an abnormally high pressure in the corresponding artery. Since the pressure in the aorta is normally more than twice as great as that in the pulmonary artery, one might think that the aortic second sound would be normally much louder than the pulmonic second sound. Such is not the case, however. Examination of healthy individuals shows that there is but little difference between the second sounds in either intensity or character. As a rule, the pulmonic second sound is relatively somewhat louder in childhood, but with advancing years the relation gradually changes until in old age the aortic sound is usually the louder.[97] The deep position of the aortic valves is hardly an adequate explanation for the relative weakness of the aortic second sound, and indeed no good explanation for it is known.

We have said that, in general, an accentuation of a second sound indicates an increase of pressure in the corresponding artery. Yet we meet cases in which increased pressure is present without an accentuation of the corresponding sound, and, conversely, accentuation of the second sound may be present without there being any increase of pressure. Other factors must come into play. Of these the proximity of the vessels

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[96] Loc. cit.

[97] Vierordt, Die Messung der Intensität der Herztöne, Tübingen, 1885; Cabot, Physical Diag., p. 123.

to the chest wall is unquestionably of importance. The wall of the artery also probably influences the sound produced, and not infrequently we observe a loud, ringing aortic second sound in arteriosclerosis of the first part of the aorta, even though there is no increase of blood-pressure.

Accentuation of the second pulmonic sound is caused by conditions which lead to an increase of pressure in the pulmonary circulation. These conditions, which have already been enumerated (see p. 43), include mitral disease, weakness of the left ventricle, pulmonary emphysema, etc The accentuation is ordinarily associated with an hypertrophy of the right ventricle, for both are caused by the increased pressure in the pulmonary artery.

Acute and chronic nephritides usually cause accentuation of the second aortic sound, and in many cases an accentuation of the second pulmonic as well. It will be recalled that this latter class of cases furnished part of the evidence which led us to assume that both ventricles do increased work in nephritis. In these renal diseases, the aortic second sound is not only louder than normal, but it frequently possesses a peculiar ringing quality, which is probably due to changes in the wall of the aorta.

Accentuation of the first sound is present in many cases of mitral stenosis, in which disease it may indeed be audible at some distance from the chest wall. The most acceptable explanation of this accentuated first sound is that it is due to a more rapid systole of the left ventricle, occasioned by the abnormally small amount of blood which this receives during diastole. This explanation receives support from the following facts. In the first place, when the right heart weakens and when correspondingly less blood is sent to the left ventricle, the accentuation of the first sound frequently becomes more marked. In the second place, a loud first sound is frequently heard after severe hemorrhage, and in this condition

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it is almost certain that the accentuation is due to a shortened, rapid systole.

The first sound is usually loud when the heart is beating rapidly. Here, again, the ventricle is incompletely filled and the contraction is rapid. Quincke[98] has described abortive contractions of the heart which follow immediately upon normal ones in which a good filling of the ventricle was an impossibility and in which the systole was short. In these the first sound was often, but not always, louder than normal. The powerful contraction of an hypertrophied heart rarely produces a loud first sound, but usually an impure and muffled one. Weak and anæmic individuals, on the other hand, frequently show surprisingly loud first heart-sounds.

In certain cases, a doubling of one or other of the heart-sounds is heard, so that three sounds may be distinguished instead of two. This is most frequently due to a reduplication of the second sounds, which may sometimes be heard even in healthy individuals, more especially at the height of inspiration. It may also be present in various heart diseases, notably in affections of the mitral valves. This reduplication of the second sound is caused by a non-simultaneous closure of the two sets of semilunar valves. It may be conceived that the difference in the time of closure is due to an unequal duration of the right and left ventricular systoles, because one ventricle must do more work than the other. Such an explanation accounts very well for the reduplication of mitral valve disease. Why it should occur in normal individuals, and why it should be absent in cases where we have reason to believe that the systole of one side is lengthened, are not so readily understood.

A doubling of the second sound is frequently heard at the apex in cases of mitral stenosis. In this case the pause between the two second sounds is longer than it usually is between

* Arch. f. klin. Med., vol. liii. p. 414.

reduplicated sounds. Possibly the extra tone is in reality a rudimentary murmur, or possibly it is produced by the auricular contraction.

Reduplication of the first sound is less common than reduplication of the second. In place of a single first sound, we hear two, the second being, as a rule, the louder. This is considered ordinarily to be due to a non-simultaneous contraction of the two ventricles, but it must be admitted that the explanation is not beyond question.

In gallop rhythm we likewise hear three heart-sounds instead of two, the extra sound being heard shortly before the usual first sound. As a rule, this extra sound is comparatively faint and muffled, and is distinctly separated from the first sound following it. This form of gallop rhythm is most frequently observed when an hypertrophied heart weakens, and above all when the hypertrophy is caused by chronic nephritis. Gallop rhythm may, however, result from arteriosclerosis, from myocarditis, and from the acute infectious diseases, and may even be present in apparently healthy hearts. It is quite probable that the extra heart-sound is produced by the contraction of the auricle. We know that the auricular contraction does produce a tone, but that in health this so immediately precedes the ventricular sound that it is merged into it and only one sound is heard for both contractions. If a pause intervene between the two contractions, then we could hear two sounds, and possibly such is the case in gallop rhythm.[99]

The quality or character of the first sound may change, but unfortunately the cause and the meaning of such changes are but little understood. A muffled or "impure" sound may be heard without there being any anatomical changes present in the valves; but, on the other hand, such an "impure" sound may herald the onset of a valvular lesion. Many such changes are possibly caused by some variation in the manner

[99] Kreige and Schmall, Ztft. f. klin. Med., vol. xviii. p. 261.

of the muscular contraction, others by changes in the tension of the valves, but as yet we cannot accurately interpret the meaning of the muffled, impure first sound.

The first sound may be fainter than normal, even though the ventricle is contracting powerfully; yet, on the other hand, a faint first sound may be due to a weakening of the ventricular contraction. I have observed a disappearance of the first sound in a case of typhoid fever in which at autopsy no macroscopical changes were found in the heart. In syncope the heart sounds are often extremely faint, and since the pulse is also very weak, we must assume that in this condition a weak heart action is responsible for the faintness of the cardiac sounds.

Cardiac Murmurs.—If the auriculo-ventricular valves allow the blood to flow back into the auricles during systole, eddies are produced by the mingling of this stream of blood with the one coming in from the great veins. These eddies set the valves in vibration very much as the violinist's bow causes the strings of the violin to tremble. Such vibrations of the valves give rise to the abnormal heart-sounds known as murmurs. In the case just described, the murmur is produced during the systole of the ventricle, and we speak of it as a systolic murmur. Such a murmur assists us in diagnosticating a leakage backward through the auriculo-ventricular opening.

If the semilunar valves are insufficient, either because they are shrunken or because the orifice is dilated, then the murmur is produced in diastole, at which period the blood streams from the aorta back into the ventricle and there causes the eddies which set the valves in vibration. The murmur may be heard throughout diastole, or it may be present only in the earlier part, at which time the negative pressure caused by the active dilatation of the ventricle most favors a leak backward from the aorta.

An obstruction to the flow of blood through any of the orifices of the heart may produce a murmur, and a simple roughening of the valves at the aortic orifice may do the same. The murmur caused by a stenosis of the mitral or of the tricuspid orifices is heard during a part or the whole of the diastole of the ventricles. When it persists throughout this period it is usually loudest at the onset and at the termination. The former accentuation is caused by the suction of the dilating ventricle; the latter by the auricular contraction. More frequently these murmurs are only heard during a part of the diastole, either at the beginning or at the end. The latter, called a presystolic murmur, precedes and runs up into the first heart-sound, and is especially characteristic of the lesion of mitral stenosis.

The murmurs produced by a narrowing or roughening of the semilunar valves are usually loud and rough. They occur at the time that the blood is passing from the ventricles into the great arterial trunks. It is sometimes possible to demonstrate that they begin somewhat later than the beginning of the cardiac impulse, for it must be remembered that the first part of this impulse corresponds to that period of the ventricular contraction during which the intraventricular pressure is being raised to the level of pressure which exists in the great arterial trunks. For this reason no blood is leaving the ventricles during the first portion of the cardiac impulse, and consequently no murmur due to an obstruction at the aortic orifice can be produced at that time.

In many cases of mitral insufficiency the first sound is well heard. It may be even louder than normal, especially if an associated mitral stenosis be present. Frequently, however, the first sound is not heard at the point of maximum cardiac impulse. In some such cases we may assume that the normal sound is overshadowed by the loudness of the murmur, but in others it seems to be absent for some other, unknown reason.

In aortic stenosis the first sound may also disappear, not only over the aortic area, but at the apex as well. The left ventricle appears to contract without producing an audible first sound. This is possibly due to the gradual and prolonged systole which is so characteristic of aortic stenosis. In aortic regurgitation the second sound may become very faint or it may disappear entirely.

Various opinions are held as to the cause of those murmurs, which have been variously designated as accidental, functional, or hæmic murmurs. They are usually systolic in time, and are most intense in the second intercostal space to the left of the sternum and at the point of maximum cardiac impulse. It is quite certain that they are not due to an endocarditis affecting the mitral valves. We cannot exclude with equal certainty, however, the presence of functional insufficiencies of the auriculo-ventricular orifice. Indeed, it appears to me that this is the cause of many of these murmurs. They are heard most frequently in weak and anæmic individuals, such as would be most liable to have a weak cardiac muscle, dilatation of the cavities of the heart, and functional insufficiency of the mitral and tricuspid orifices. The second pulmonic sound is frequently found to be accentuated, which would also favor the idea that there is some damming back in the pulmonary circulation. It seems improbable that all functional murmurs are produced in the manner described, for many are not accompanied by an accentuation of the second pulmonic sound.

Diastolic functional murmurs, which simulate the murmur of aortic insufficiency, are very uncommon. Most of these are probably produced in the great veins, and are simply transmitted to the precordium.[100] Some, however, cannot be thus explained.

Palpitation.—Palpitation of the heart has been defined as

[100] Cabot and Locke, Johns Hopkins Hosp. Bull., May, 1903.

an irregular or forcible heart action perceptible to the individual himself. In health, we are not ordinarily conscious of the action of our hearts, unless this action is much increased by exertion or by excitement. It seems probable that there are sensory nerves in the heart or in its vicinity which are stimulated under these circumstances. Pathological palpitation may be due either to an abnormal heart action or to an increased sensitiveness of these nerves, rendering the individual abnormally conscious of his heart's action. Naturally both causes may be operative in the same individual.

An increased heart action does not necessarily produce the sensation of palpitation. This fact is frequently illustrated in cases of valvular disease, and is perhaps to be explained on the assumption that the gradual development of the condition allows the sensory nerves of the heart and adjacent structures to become accustomed to the changed conditions. Not infrequently, however, patients with hypertrophy and dilatation of the heart suffer from palpitation, especially during any exertion. In such cases the heart is working up to the limits of its capabilities, and possibly the increased tension of the cardiac wall stimulates the sensory nerves, and so produces the sensation of palpitation.

In yet other individuals, no definite connection between the heart's action and the palpitation can be discovered. This is especially true of the palpitation associated with anæmia and that due to certain poisons, notably tobacco, tea, and coffee. In such cases it is possible that the systole is modified, but it seems more probable that the patient is conscious of his heart's action merely because of an increased irritability either of the cardiac nerves or of their centres.

Cardiac Dyspnœa.—Shortness of breath is a very frequent symptom of heart diseases. It is often associated with a sensation of oppression about the chest or with a general feeling of anxiety, but it may occur alone. It may vary

greatly in degree, from the slightest dyspnœa on exertion to the most extreme air-hunger, even when at perfect rest. This symptom is not characteristic of any one form of heart disease, but occurs whenever the interchange of gases in the lungs is seriously interfered with. Periodic interference with the interchange of gases leads to periodic dyspnœa, the so-called cardiac asthma.

The dyspnœa of heart disease is always due to an insufficient interchange of gases between the blood and certain cells of the medulla. (See Chapter V.) Two causes are directly responsible for the dyspnœa of heart disease. The first is the slowing of the blood-stream, which diminishes the interchange of gases in the lungs and in the respiratory centre of the medulla. Any slowing of the blood-stream in the lungs beyond a certain limit leads to an insufficient interchange of gases. (See Chapter V.) A second cause for the dyspnœa of heart disease lies in the changes which take place in the alveolar epithelial cells of the lungs. These changes, which have already been described (see p. 58), would undoubtedly interfere with the interchange of gases in the lungs, even though the blood-stream were not retarded.

The dyspnœa which develops only when the patient exerts himself is due to a relatively slow circulation, the rate of flow not being increased proportionately to the demands for fresh blood. Indeed the exertion may cause a fall of arterial pressure in patients with heart disease.[101]

The term cardiac asthma is applied to those paroxysms of extremely severe dyspnœa which occur in individuals who have heart disease. The dyspnœa is often of the most extreme grade, and may be accompanied by excessive anxiety and a terrible sense of impending death. The paroxysms may begin after a meal, after exercise, during the night, or without any apparent cause. They occur most frequently in those who

[101] Buttermann, Arch. f. klin. Med., vol. lxxiv. p. 1.

have arteriosclerosis or chronic nephritis. During the attack, the pulse is usually rapid, soft, and irregular in force and frequency. The blood-pressure is usually lower than normal. The most frequent cause of cardiac asthma is a transient weakness of the left ventricle. This raises the pressure in the pulmonary vessels, and so increases the work of the right heart. If the latter is unable to accomplish the additional work so thrown upon it, there results a diminution in the velocity of the general blood-current. It is difficult to say to what extent the universal and sudden overfilling of the pulmonary capillaries contributes toward the production of the symptoms. In certain cases the dyspnœa becomes less when the right heart weakens. Since the pulmonary capillaries would then be less distended, this favors the view that the distention of the capillaries is to some degree responsible for the paroxysms of dyspnœa.

Patients suffering from heart disease frequently develop dyspnœa from pulmonary complications, such as bronchitis, pneumonia, and œdema, to which diseases they are, indeed, peculiarly subject.

In the French literature, many other causes for the dyspnœa of heart disease are enumerated, among which are toxic and reflex influences. At present, however, there is little real proof for the existence of such causes.

Cardiac Pain.—As has already been stated, a feeling of intense anxiety often accompanies cardiac dyspnœa. This feeling may occur alone, or it may be associated with pain in the precordium. The latter, however, rarely occurs alone, except in nervous individuals, in whom the pain is of psychic origin and is simply referred to the periphery.

Cardiac pain, originating in the heart itself, is seen especially in disease of the coronary arteries and of the first part of the aorta. It accompanies aortic more frequently than mitral lesions, because the former are more frequently asso-

ciated with arteriosclerosis. Patients with various forms of
myocarditis also frequently complain of pain about the heart
and of cardiac distress, which sensations may either be con-
stantly present or may occur in paroxysms.

The severity of the pain varies greatly. On the one hand,
the patient complains of sensations which trouble him mainly
because they are unusual, while, on the other hand, the pain
is of such indescribable severity that death seems imminent.
It is not the place here to enter into a description of the
clinical features of these cases of angina pectoris. They occur,
almost without exception, in those who have sclerosis of the
coronary arteries. The attack may come on without any
apparent cause, but usually it is precipitated by some unwonted
excitement, by overexertion, or by digestive disturbances.
Most of the attacks are due to cardiac weakness induced by
these unfavorable circumstances.

We do not know what causes the pain of angina pectoris.
Arteriosclerosis of the coronary arteries is certainly present
in most cases, frequently causing a narrowing of the lumen
of the vessel.[102] Perhaps it is the anæmia of certain parts
of the heart which causes the pain. Such a theory finds an
analogy in the condition known as intermittent claudication,
in which, owing to a narrowing of the arteries, pains and
disturbances of function develop in the legs whenever the
patient walks some little distance.[103] In some cases the
anginal paroxysms cease, and this has been attributed to a
reopening of the vessel, although we have no proof for such
an hypothesis. Breuer[104] calls attention to the fact that we
are not yet perfectly clear even about intermittent claudication,
for we do know how great a rôle spasmodic contraction of
the arteries may play in this condition. Nothnagel[105] believes

[102] Curschmann, Kongr. f. in. Med., 1891, p. 275.
[103] Erb, Münch. med. Wochenschr., 1904, p. 905.
[104] Münch. med. Wochenschr., 1902, Nos. 39–41.
[105] Ztft. f. klin. Med., vol. xix. p. 209.

that the pain may originate from the vessels themselves. Such an hypothesis, attributing the pains of angina directly to the spasmodically contracted vessel, is very attractive. It would explain the fact that these paroxysms of pain may occur without anatomical disease of the coronary vessels, as has been observed in nervous individuals and especially in those who use tobacco to excess. Many other questions in relation to angina are still unanswered, as, for example, the reason why the pains radiate to the left branchial plexus, the cause of the syncope in some cases, and finally the cause of the sudden death. Every attack of true angina is a menace to the life of the individual, and not infrequently the patient dies during the attack. In only one other condition do we see an equally sudden death, and that is in coronary embolism. The body may be found in the exact position that it was in when the attack of angina began. No signs of asphyxia are present. The cause of sudden death has never been explained.

CHAPTER II.

THE BLOOD-VESSELS AND THE LYMPH.

THE condition of the arterial walls and the width of the arteries exercise a considerable influence upon the flow of blood. If the arteries were all fully dilated, it would be absolutely impossible for the heart to maintain the circulation, for the relatively small quantity of blood in the body could not properly fill the vessels. The width of the arteries is regulated mainly by reflexes coming from various parts of the body. Stimulation of a peripheral nerve will normally cause a reflex arterial constriction and will raise the blood-pressure; and nervous impulses from the heart are also able to affect the size of the blood-vessels, and so in a measure to regulate the work of that organ.

We have stated that the degree of contraction of the arteries, their tonus, is mainly dependent upon the nervous impulses that they receive. Though recent observations have demonstrated an independent muscular tonus in the blood-vessels, this seems to play a very small part in health and disease.

If the arteries leading to a certain part of the body dilate or contract, the blood-supply to that part will be altered. These changes are fully discussed in the ordinary text-books on physiology and pathological anatomy, and need not be dwelt upon here. It is necessary to remember, however, that, if the tonus of extensive vascular areas is altered, the effect is not easily neutralized by a change of tonus in the opposite direction in other parts of the vascular system, and that then the total peripheral resistance and perhaps the blood-pressure will be affected. For this reason, the condition of the numerous abdominal vessels, innervated by the splanchnic nerves, is of

primary importance in the maintenance of the peripheral resistance, and it is quite possible that the cutaneous vessels likewise play an important rôle in man.

The Arterial Blood-Pressure.—(The blood-pressure in the larger arteries is dependent mainly upon two factors.—the amount of blood pumped into the arterial system by the heart, and the resistance offered to the escape of blood from this system through the smaller arteries and capillaries. Of less importance is the elasticity of the vessel walls and the total quantity of blood in the body. These various factors, influencing blood pressure, may interact upon each other in the most complicated manner. For example, if the arterial pressure be increased from any cause, the vagus nerve is stimulated, with the result that the heart is slowed and less blood is delivered into the aorta. In a like manner, when the volume of blood is rapidly changed, the blood-vessels change their caliber, so that, within certain limits, the blood-pressure is not altered.

Systolic and Diastolic Pressures. The Pulse-Pressure.— The arterial pulse is caused essentially by the variations of pressure within the artery, produced by the intermittent expulsion of blood from the heart. The highest point on this wave of arterial pressure is called the systolic pressure, and the lowest point the diastolic pressure. The difference between the two—*i.e.*, the variation of pressure with each pulse—is called the pulse pressure. Thanks to modern instruments, it is now possible to determine these pressures with a fair degree of accuracy upon man by indirect methods.[1]

The factors which influence the blood-pressure as a whole have been mentioned in the preceding paragraph. Of special interest, however, are the factors that affect the difference between the systolic and the diastolic pressure,—*i.e.*, the pulse-pressure. It is theoretically possible that this should be in-

[1] See Janeway, Clinical Study of Blood-Pressure, p. 77; Erlanger, Am. Jour. of Physiol., vol. x.

fluenced in at least three ways. An increase in the amount of blood delivered at each beat from the heart into the aorta would tend to increase the difference between the diastolic and systolic pressures. On the other hand, a rapid emptying of the blood-vessels would likewise tend to increase this difference, independently of whether the extra blood flowed through the capillaries into the veins, or whether it regurgitated into the heart owing to an aortic insufficiency. It is obvious that the amount of blood pumped into the arteries and the amount which escapes from them in both directions must, in the long run, be approximately equal, for otherwise large amounts of blood would accumulate in, or disappear from, the arteries, as the case might be. Finally, the rigidity of the arterial walls will exert an influence upon the pulse-pressure. If the arteries were absolutely rigid tubes, the heart would be compelled to move the whole column of blood with each beat, and between beats the flow would stop entirely. There would therefore be a high pressure in the arteries during systole and practically no pressure during diastole, and the pulse-pressure, or the difference between the two, would be exceedingly high. There is reason to believe that slighter changes in the rigidity of the arteries will affect the pulse-pressure in a similar though less marked manner, and patients with arteriosclerosis frequently show high pulse-pressures.[2]

Some authors have attempted to estimate from the pulse-pressure the total output of blood from the heart, yet it is obviously impossible to do this so long as we cannot allow for the effect produced by the elasticity of the arterial walls, which latter varies not only in different individuals from such causes as arteriosclerosis, etc., but probably can also vary in the same individual under different conditions of absolute blood-pressure and of fulness of the artery. In spite of these objections, however, it is possible that the determination of the pulse-pressures

[2] A. D. Hirschfelder, Personal Communication.

will in the future furnish us with valuable data as to the quantity of blood being propelled by the heart.

Physiological Variations in Blood-Pressure.—Age influences the blood-pressure. During the first year of life the systolic pressure usually ranges between 75 and 90 mm. of mercury, in adults it is usually 100 to 130 mm., and in old people 130 to 145 mm.[3] Excitement generally causes a most marked rise of pressure. Muscular exertion will also usually increase the systolic pressure, though this increase is less marked when the individual is expert in performing any particular act, and, indeed, it may then not take place at all. During exercise the difference between the systolic and diastolic pressures is often quite markedly increased, an indication, apparently, of the larger quantity of blood delivered by each systole of the heart. In the early hours of sleep, there is quite a marked fall in the mean blood-pressure, which gradually rises toward morning.[4]

Pathologically Increased Blood-Pressure.—Certain drugs may raise the blood-pressure either because they act mainly upon the heart, as does digitalis, or because they tend to cause a constriction of the blood-vessels, as does adrenalin. Acute asphyxia or acute anæmia of the medullary centres of the brain will stimulate the vasomotor centre most powerfully, producing a contraction of the splanchnic vessels and a great rise of arterial pressure. Such a cerebral anæmia appears to be the cause of the extremely high blood-pressures sometimes seen in cases of acute cerebral compression, a subject which will be discussed in another place (p. 450). Lead colic is usually associated with a high arterial pressure, and the early stages of peritonitis are likewise frequently accompanied by such a rise. Pain, even that caused by pinching the skin, usually increases the systolic pressure in healthy individuals.

[3] Janeway, loc. cit , p. 128.
[4] Brush and Fairweather, Am. Jour. of Physiol., vol. v. p. 199.

Continuous high pressure is seen in certain forms of renal disease (see p. 50). It may also accompany arteriosclerosis of the first part of the aorta or of the splanchnic vessels (p. 46). —Ed.)

The effect of an increased peripheral resistance upon the general circulation depends for the most part upon the behavior of the left ventricle. If this were to act in an ideal manner, it would contract more forcibly, and so, by raising the general arterial pressure, would overcome the increased resistance. Unfortunately, however, when the peripheral resistance and the arterial pressure are much increased, the left ventricle does not empty itself completely, the pressure in the left auricle rises, and a retardation of the blood-flow through the lungs takes place.

Pathological Diminution in Blood-Pressure.—Widespread dilatation of the blood-vessels may lead to a serious fall of arterial pressure and a slowing of the circulation, for, as we have said, the total quantity of blood in.the body is insufficient to fill the blood-vessels properly if they are all widely dilated.

Such a wide-spread dilatation may result from a general loss of arterial elasticity with stretching and widening of the blood-vessels. This has been observed in certain cases of aortic insufficiency (p. 59) and in the late stages of arteriosclerosis (p. 46).

Arterial dilatation may also result from a wide-spread loss of arterial tonus. Thus, if the splanchnic vessels lose their tone, they become filled with blood, and the arteries to the other parts of the body, especially to the skin and muscles, are left comparatively empty. The patient becomes weak and pale, the arterial and venous pressures fall, and the heart receives an insufficient supply of blood. The pulse becomes soft and rapid, and finally syncope supervenes. Such a patient is practically bled into his own abdominal vessels, and life may last only a few hours or even minutes. If other arteries, in addition to

the splanchnic vessels, are dilated, the symptoms are intensified; yet the condition of the splanchnic vessels is of paramount importance on account of their great capacity.

A clinical picture, similar to that just described, may be produced by toxic doses of such drugs as chloral and alcohol, both of which will ultimately paralyze the vasomotor centre. A similar picture is also presented by the so-called collapse that sometimes occurs during the course of infectious diseases. These symptoms are not those of ordinary heart failure, for the pulmonary congestion and the stasis in the veins of the general circulation are both lacking. The picture seems rather to be caused by an insufficient supply of blood without stasis, and it may be interpreted as an extensive vasomotor paralysis.

This question has been carefully studied on animals.[5] The great falls in pressure which occur at the height of experimental infections with the pneumococcus, the diphtheria bacillus, and the bacillus pyocyaneus, have all been shown to be due to a paralysis of the vasomotor centres. In pneumococcus infections, the heart may beat with more than its usual force, and may thus, to a certain degree, compensate for the loss of vasomotor tone. In diphtheria infections, however, the heart is usually also injured, and some, indeed, claim that the injury to the heart is here the most important cause of the circulatory disturbances.[6] It has also been definitely proved that in a perforative peritonitis, experimentally induced, the cause of death is a toxic paralysis of the vasomotor and respiratory centres.[7]

To what extent these experimental results are applicable to man is somewhat uncertain. It is difficult to determine clinically whether the symptoms are due more to a cardiac weak-

[5] Romberg, Pässler, Bruhns, Müller, Arch. f. klin. Med , vol. lxiv. p. 652; Pässler and Rolly, ibid., vol. lxxvii. p. 96.
[6] Steyskal, Ztft. f klin. Med., vol. xliv. p 368, and vol. li p 129.
[7] Heineke, Arch. f klin. Med., vol. lxix. p. 429.

ness or a vasomotor paralysis. Personally I am inclined to believe that both are at fault in most instances of circulatory failure during the course of acute infectious diseases.

(The term " surgical shock" has been used to designate a peculiar depression of the activities of the central nervous system, which is ordinarily caused by very severe traumatism to the peripheral nerves. A slight or moderate traumatism to these nerves will ordinarily cause a rise in blood-pressure; if, however, the injury be particularly severe or many times repeated, or if the patient be weakened by anæmia, etc., then the result of the traumatism is a fall in blood-pressure, and the symptom-complex of shock is produced. Crile's exhaustive experiments [8] would seem to indicate that surgical shock is caused by an exhaustion of the vasomotor centre, which renders it unable to maintain the tonus of the arteries. The fall of blood-pressure is due, therefore, to a vasomotor paralysis, and the condition resembles in many particulars the collapse that may occur during the acute infectious diseases.—ED.)

The Arterial Pulse.—The arterial pulse is produced mainly by changes of pressure within the arteries, caused by the intermittent expulsion of blood from the heart. In general, the frequency and rhythm of the pulse is the same as that of the heart, yet we must remember that some of the heart's beats may not reach the wrist, and that some may be retarded more than others in their passage to the periphery. Lesions of the heart may modify the form of the pulse, as is well illustrated in the typical pulses of aortic stenosis and aortic insufficiency; and the form of the pulse is also affected by the condition of the vessel wall. Many secondary waves on the main pulse-wave can be demonstrated by pulse tracings. Some of these are due to instrumental defects, and some to changes in the heart and vessels. Indeed, so many factors influence the form of the pulse-curve that it is usually quite impossible to draw any satis-

[8] Blood-Pressure in Surgery, 1903.

factory conclusions from this form.   We shall therefore omit
a discussion of this subject.

<center>THE VEINS.</center>

Venous Stasis.—It has already been shown that stasis of
the blood in the veins may result from cardiac weakness.   The
stasis in the pulmonary circulation, produced by a weakness of
the left ventricle, may be overcome to a certain extent by the
increased activities of the right ventricle, whereas the stasis in
the veins of the general circulation, resulting from a weakness
of the right ventricle, cannot be thus overcome, and the entire
blood current is slowed.

General venous stasis may also be caused by diseases of the
lungs or by pressure upon the great veins.   If the intrathoracic
pressure be increased, either by a diminution in the elasticity
of the lungs (emphysema) or by a collection of fluid or gas
in the pleural cavities, or if the thoracic movements are les-
sened, as happens during superficial breathing, then a diminu-
tion in the flow of blood to the heart results.   Pressure upon
the great veins by tumors and especially by pericardial effu-
sions may also interfere with the return of venous blood to the
heart.   A pericardial effusion may, indeed, cause sudden death
by compressing the venæ cavæ just before their entrance into
the right auricle, and so shutting off the entire blood-supply
to the heart.

Venous Murmurs.—In certain individuals, especially in
chlorotic girls, a murmur may be heard over the bulbus jugu-
laris.   This is usually louder on the right than on the left side,
and is known as the venous hum.   Its cause is not well under-
stood.   Some believe that it is a murmur of stenosis caused by
the passage of the blood from the external jugular vein into the
jugular sinus, yet why this should occur especially in anæmic
individuals is not known.   Sahli[9] considers that the blood

[9] Klin. Untersuchungsmethoden.

flows more rapidly in anæmia, and that this is the cause of the murmur; yet it has not yet been satisfactorily proved that the blood-flow in anæmic individuals is really more rapid.

THE MOVEMENTS OF THE LYMPH.

The lymph may be looked upon as the fluid that has escaped from the capillaries. It carries material to the cells of the parenchyma, and, laden with waste products, returns to the blood again by way of the lymphatic vessels. Its composition, therefore, varies according to the organ from which it comes and according to the activity of that organ.

We know of no disease in which too little lymph escapes through the capillary walls, although it seems probable that such do exist.

Œdema.—Certain conditions lead to an accumulation of lymph in the lymphatic vessels and spaces, among which latter the serous cavities may be included. Theoretically, such accumulations may be brought about, first, by an excessive formation of lymph; secondly, by a hinderance to the escape of lymph; and thirdly, by a combination of the two. The quantity of fluid that passes through the capillary walls depends, on the one hand, upon the difference in pressure between the blood in the capillaries and that of the lymph in the surrounding tissues, and, on the other hand, upon the permeability of the capillary walls themselves.

Œdema from Stasis.—Œdema may be caused by a stasis of blood in the veins. This stasis may be merely local, as when it is caused by an occlusion of a vein by thrombosis or external pressure; or it may be general, as when it results from pathological changes in the lungs, weakness of the right heart, intrathoracic tumors, and pleural or pericardial exudates. The œdematous fluid that collects in the lymph-vessels and spaces in such cases, is poorer in proteids and leucocytes, but richer in erythrocytes, than is normal lymph. The organs that be-

come most swollen are those in which the tissues are under the least elastic tension and in which the venous stasis is favored by gravity. For this reason the œdema caused by general stasis is usually first observed about the ankles and over the lower part of the back.

The mere obstruction of a vein does not necessarily lead to œdema, for a collateral venous circulation may be established. After the experimental ligature of a vein, the occurrence of œdema is greatly favored by the frequent accompanying arterial hyperæmia.

Even an increased transudation of lymph does not necessarily cause an œdema, for the excessive amount may be carried away by the lymphatics. There must, therefore, be, in addition, some interference to the lymph-flow from the part. When general venous stasis causes the œdema, the blood-pressure in the left subclavian vein is naturally raised, and this would furnish the interference to the flow of lymph into this vein from the thoracic duct.

The lymph-flow may also be hindered in other ways. An increased pressure in the capillaries is transmitted to the tissues about them, which latter gradually become stretched and lose their elasticity.[10] This loss of elasticity diminishes the pressure normally exerted by the tissues upon the lymph-spaces, the difference between the blood- and the lymph-pressures is therefore increased, and exudation is favored. On the other hand, the diminished pressure exerted by the tissues upon the lymph-spaces tends to lessen the rate of lymph-flow from the tissues toward the thoracic duct. For these reasons, the elasticity of the tissues exercises a most important influence upon the occurrence of œdema, and different organs become swollen to different degrees, even though they all are exposed to the same venous stasis.

The mere obstruction of a lymphatic vessel rarely leads to

[10] Landerer, Die Gewebsspannung, Leipzig, 1884.

œdema, on account of the numerous anastomoses between the lymphatics. If, however, the thoracic duct be obstructed, ascites and œdema of the legs usually develop.

Inflammatory Œdema.—As is well known, inflammations injure the walls of the capillaries. There is an active local hyperæmia, and, at the same time, a slowing of the blood-current caused by the changes in the vessel walls. These walls influence the amount and character of the transudate, and consequently the lymph of inflammation differs from that normally transuded, in that it contains more albumin and more numerous blood-corpuscles. Purulent inflammations are characterized by the richness of their exudates in leucocytes, which latter are attracted thither by the primary cause of the inflammation.

Inflammatory processes also interfere with the removal of lymph from the tissues, for they directly diminish the tissue elasticity, with the results just described. Even the elasticity of tissues at some little distance from the inflammation may be diminished, so that these also become œdematous, thus producing the so-called collateral œdema.

Nephritic Œdema.—Of the dropsies that accompany nephritis, some are unquestionably due to simple stasis. We have seen that the heart is often weakened in nephritis, and it is obvious that this may cause the ordinary dropsy of heart disease. We wish here, however, to consider those nephritic œdemas that occur independently of any cardiac weakness. They usually first appear in the subcutaneous tissues, and especially in those that possess the least tension, as about the ankles and eyelids, though not infrequently the great serous cavities are early filled with fluid.

Œdema of this character is rarely seen in certain forms of nephritis, especially in chronic interstitial nephritis, in the nephritides caused by certain poisons (arsenic), and in those associated with certain infectious diseases (pneumonia and typhoid fever). On the other hand, œdema is common and

often of a most marked grade in chronic parenchymatous nephritis, in amyloid kidney, in scarlatinal nephritis, and in primary acute nephritis.

The urine in these cases is frequently diminished in amount and rich in albumin; yet the high percentage of albumin can hardly be the cause of the œdema, for large quantities may be excreted with comparatively slight œdema, as sometimes happens in amyloid disease of the kidney. Furthermore, a reduction of the albumin in the blood cannot be the sole cause of the œdema, for we know that with plenty of food there is no diminution of albumin in these cases When cachexia develops, the albumin may, indeed, be diminished and œdema may appear, but this œdema is of a different character and is of relatively slight extent.

It is possible that the œdema of nephritis is produced by a primary retention of water in the body. In the forms of the disease under consideration, less urine than normal is usually secreted, and frequently the œdema increases as the urine diminishes, and *vice versa*. Many writers, therefore, favor the view that a primary retention of water in the bodies of these patients dilutes their blood and so produces an hydræmia or an hydræmic plethora; and Hammerschlag has shown [11] that a diluted blood is usually present in these cases of nephritis. Nevertheless, the theory has many opponents. Most experimenters have failed to produce an œdema by the mere infusion of salt solution. Half of the blood has been withdrawn and replaced in this manner and enormous quantities of fluid have been infused without producing any œdema.[12] Some other factor, therefore, seems to be necessary, and this is possibly an injury to the vessel wall. Magnus has discovered a whole series of substances which will produce extensive anasarca if

[11] Ztft. f. klin. Med., vol. xxi. p. 475.

[12] Cohnheim and Lichtheim, Virch. Arch., vol. lxix. p. 106; Magnus, Arch f. exp. Path, vol xlii p 250

injected into an hydræmic animal. Among these are substances that are retained in the body after removal of the kidneys.

One may assume, therefore, that some change in the capillary walls is, in part, responsible for the œdema of nephritis, though up to the present these changes have not been demonstrated anatomically. We have already seen that such hypothetical changes in the blood-vessels probably account for the cardiac hypertrophy in certain cases of nephritis. The œdema of nephritis is therefore explainable on the theory of primary retention of water in the body combined with an injury to the walls of the blood-vessels.

The relation of the tissues to the œdema of nephritis is not well understood. Their elasticity might be primarily diminished or their osmotic pressure might be increased, and in either case a retention of fluid could result.[13] These are possibilities which open a new field for investigation.

(Some nephritic œdemas apparently depend upon the retention of sodium chloride in the body. The normal individual excretes this salt at about the same rate as it is ingested, so that the amount in the body remains nearly constant. In nephritis, on the other hand, the excretion frequently does not follow the same curve as the ingestion.[14] The French school, especially, has explained certain cases of nephritic œdema on the basis of a retention of chlorides in the body. According to this hypothesis, the inability of the kidneys to eliminate sodium chloride leads to a retention of this salt in the body, and this retention, in turn, necessitates an accumulation of water in the tissues in order to maintain the proper osmotic relations. In some cases of nephritis,[15] truly wonderful results have followed variations in the amount of common salt taken in the food. When large

[13] Strauss, Ztft. f. klin. Med., vol. xlvii. p. 337; Koziezkowsky, ibid., vol. li. p. 287.

[14] Halpern, Festschrift f. E. Salkowski, Berlin, 1904.

[15] See, for example, that reported by Widal and Javal, International Clinics, Fourteenth Series, vol. i. p. 1.

quantities were given to such patients, the kidneys did not excrete all of it, the weight of the body rapidly increased owing to the accumulation of water, and when this increase had reached a certain limit, œdema appeared. If now the sodium chloride in the diet were so reduced that the output exceeded the intake, then the water retained in the body was rapidly excreted and the œdema disappeared. Other variations in diet, such as changes from milk to meat, etc., did not influence the œdema, except in so far as they were accompanied by changes in the quantity of common salt taken. From these observations, it seems very probable that certain nephritic œdemas depend upon a primary, insufficient elimination of sodium chloride by the kidneys.—ED.)

Other Œdemas.—We know little concerning the dropsies caused by severe cachexias and by many diseases of the cord and of the peripheral nerves. Changes in the composition of the blood probably contribute to the causation of the former, while in the latter, paralyses of the muscles would interfere with the movements of the lymph and so tend to produce œdema. Yet in neither case do these seem to be the sole causes.

Composition of Exudates.—The composition of exudates varies with their origin.[16] Those due to inflammatory causes usually contain four per cent. of albumin or over, while those due to other causes usually contain between 0.1 and 0.8 per cent. The exudates that are poorest in albumin are those caused by cachexias and by chronic nephritides, a percentage less than 0.1 being rarely found except in serious renal disease, especially in amyloid disease of the kidney.

Chylous and Chyliform Ascites.—Exudates into the peritoneal cavity, and more rarely those into the pericardial and pleural cavities, may contain considerable amounts of fat. This may arise from a fatty degeneration of the cells of the exudate, with subsequent disintegration of these cells. When

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[16] Hoffmann, Arch. f. klin. Med., vol. xliv. p. 413.

the blood contains such large quantities of fat, the latter sometimes passes through the capillary walls into the exudate. Such exudates into the peritoneal cavity are called chyliform ascites.[17]

In another group of cases, usually caused by carcinomata, the abdominal lymphatics rupture and the chyle flows directly into the peritoneal cavity, producing the so-called true chylous ascites. The composition of the ascitic fluid then depends largely upon the character of the food, and when certain fats are ingested, they may be demonstrated in the ascitic fluid.[18] During life it is often impossible to differentiate these two forms of ascites.

Pulmonary Œdema.—Œdema of the lungs may result from the same causes as does œdema of other parts of the body. The exudation about an inflammatory area corresponds to the inflammatory œdema already described (p. 118). On account of the rich and peculiar blood-supply of the lungs, however, a local œdema from stasis does not occur. If there be a hinderance to the blood-flow through one part of the lungs, the blood merely takes another course. No sharp line can be drawn between local inflammatory œdema of the lungs and a small pneumonic patch.

Of great interest is the cause of the general pulmonary œdema that so frequently terminates cardiac, pulmonary, and infectious diseases. Two hypotheses have been advanced in explanation of this œdema. The first considers that it is caused by stasis. If, experimentally, the left ventricle of an animal be seriously injured while the right is left intact, then pulmonary œdema frequently develops.[19] The œdema in such instances is evidently caused by stasis, and we have reason to

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[17] Bargebuhr, Arch. f. klin. Med., vol. li. p. 161; Pagenstecher, D., Ztft. f. Chir., vol. lxii. p. 312; Mutermilch, Ztft. f. klin. Med., vol. xlvi. p. 123.

[18] Minkowski, Arch. f. exp. Path., vol. xxi. p. 373.

[19] Cohnheim and Welch, Virch. Arch., vol. lxxii. p. 375.

believe that at least some pulmonary œdemas of man have a like causation. This, in all probability, is the cause of the œdema that sometimes develops after sudden, severe injury to the left heart, such as may be produced, for example, by an acute aortic insufficiency.

In order to produce this œdema experimentally, it is necessary that the left ventricle should be almost completely paralyzed; for if it be only relatively weakened, no œdema of the lungs ensues.[20] Now the general arterial pressure of patients with pulmonary œdema, especially when the latter follows nephritis or arteriosclerosis, rarely reaches the low level that is experimentally necessary, and in these patients there is certainly no complete paralysis of the left ventricle. Sahli, therefore, believes that general pulmonary œdema results, in most instances, from changes in the capillary walls. A number of facts support this view. First, the œdema is unevenly distributed throughout the lungs; and secondly, it is often associated with definite inflammatory processes. Indeed, in heart disease, no sharp line can frequently be drawn between the œdematous areas and the pneumonic patches that are so frequently encountered. Some œdemas of the lungs are therefore almost certainly of an inflammatory nature. Possibly future observations on the percentage of albumin in the œdematous fluid will give some indication as to the nature of its cause.

Though it must be acknowledged that inflammatory processes do contribute to the production of certain pulmonary œdemas, nevertheless it seems to me that the weakness of the left ventricle is of, at least, equal importance in most cases. The results of animal experimentation are not directly applicable to man. The chronic pulmonary stasis that accompanies heart and kidney diseases may induce changes in the walls of the capillaries of the lungs, so that a relatively slight weakness

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[20] Sahli, Ztft. f. klin Med., vol xiii. p 482; Arch f. exp. Path., vol. xix. p. 433.

of the left ventricle could produce œdema, which would not be the case if the vessels were entirely healthy. Not infrequently the physician sees patients in whom a weakening of the left ventricle is followed by an œdema of the lungs and a subsequent strengthening of the ventricle by a disappearance of the œdema.

CHAPTER III.

THE BLOOD.

General Considerations.—The pathology of the blood is intimately connected with that of every individual organ in the body; for it is the connecting link between all of them, receiving material from and giving material to each. Its constitution depends, therefore, to a great extent, upon the condition of the various parts of the body. It contains a great variety of substances; yet the rapidity of the blood-current, the minute quantities of many of these present, and the rapid excretion of those which are present in excess allow the blood to maintain a fairly constant composition.

It is improper to designate any one or any several organs as the blood-forming organs. Every tissue in the body furnishes its contribution to the blood, and when an organ is spoken of as a blood-forming organ it is usually meant that it gives to the blood some of its more striking elements, the blood corpuscles.

From what has been said, it will be seen that the composition of the blood will change whenever there are pathological changes in the activity of any organ that furnishes metabolic products to the circulation. Viewed from this stand-point, there are a great number of blood diseases, among them diabetes and the majority of hepatic and renal disorders. Clinically, however, it is customary to speak of diseases of the blood only when the changes in the blood dominate the pathological picture, or when the cause of the blood changes is unknown. Whether, in the latter class of cases, the blood changes are really primary or not is a question that cannot at present be definitely decided.

Changes in the blood-cells and in the hæmoglobin are recog-

nized with comparative ease, and consequently they are better known than are the changes in the composition of the plasma.

ANÆMIA.

Although the term anæmia is used to designate those conditions in which the hæmoglobin or the red blood-corpuscles, or both, are reduced, it should not be assumed that these are the only changes of consequence in anæmic blood. Other alterations, of perhaps equal importance, take place in other constituents, and a satisfactory understanding of anæmia will only be possible when we shall have become acquainted with all these various changes. For example, the integrity of the red corpuscles is intimately dependent upon the molecular concentration of the plasma. If they be placed in solutions which contain either too large or too small a quantity of salts, they become either shrunken or swollen, and in either case they may lose their hæmoglobin. The proteids of the plasma also seem to have some influence upon the property of the red cells to retain their hæmoglobin; and the presence of certain poisons in the blood will undoubtedly cause a discharge of the hæmoglobin from the stromata of the corpuscles.

Anæmia from Hemorrhage.—Anæmia may be due to an acute hemorrhage. If the loss of blood exceed a certain limit, which is about fifty per cent. of the total quantity, then the amount left in the vessels is insufficient for the maintenance of the circulation, and the patient dies with all the symptoms of acute asphyxia, owing to the insufficient supply of blood to the tissues and especially to certain parts of the brain. This subject of acute asphyxia will be discussed in the chapter on respiration.

If the hemorrhage does not exceed this limit, the fluid portion of the blood lost is rapidly replaced by fluids from the tissues and food. The proteids and the corpuscles are replaced more gradually by an increased functional activity on the part

of the tissues which furnish them; and finally, after weeks, or perhaps months, the blood regains its normal composition. During the first few hours after a hemorrhage, therefore, the blood, as a whole, is reduced in quantity. Then follows a dilution of that present with lymph; and after this there comes the regeneration of the red corpuscles. The regenerated corpuscles are often smaller than normal, but some may be enlarged and a few of them may contain nuclei. For a considerable period after the hemorrhage, the individual corpuscles contain less hæmoglobin than do normal ones, for this pigment is regenerated comparatively slowly, and for some time, therefore, the proportion between the percentage of hæmoglobin and the number of red corpuscles remains less than the normal proportion. The leucocytes in the peripheral blood are usually increased in number for a short period after the hemorrhage. The rapidity with which the blood is regenerated depends in part upon the amount of blood lost, in part upon the general nutrition of the patient, and in part upon the treatment which he receives.

General Considerations Relative to the Chronic Anæmias. —In the chronic anæmias the blood does not return so quickly to the normal, because the cause of the anæmia remains operative. This cause may injure either the blood-forming organs or the blood-corpuscles already formed. It is well known that the blood of one animal may destroy the corpuscles of another, and we must admit the possibility that similar toxic substances may develop in the body under pathological conditions. Indeed, there is evidence that this does occur in certain diseases.[1] Various poisons, such as chloroform and potassium chlorate, exert a similar injurious action upon the red blood-cells. It is also possible that an anæmia may be produced by an acceleration of the normal destruction of the red blood-cells, which becomes so rapid that the normal regenerative processes cannot

[1] Maragliano, Kongr f in. Med., 1892, p. 152.

keep pace with it. Practically the same condition is produced when repeated, small hemorrhages take place, for here again the loss of blood may be so great that the normal regenerative processes cannot supply the deficiency.

On the other hand, the anæmia may arise, not from an excessive loss or destruction, but from an insufficient formation of red blood-corpuscles, and it is often extremely difficult in the individual case to determine which of the two is primary. An increase in the amount of iron deposited in the liver would indicate an increased destruction of red corpuscles. This organ normally contains a small amount of iron, but in anæmia the amount is often greatly increased; and not infrequently the spleen, kidneys, and bone-marrow also show abnormal deposits of iron salts. In the anæmias that are caused, not by destruction, but by losses of blood through hemorrhage, such deposits do not occur;[2] and, indeed, the iron normally present in the tissues may be reduced, for it is utilized in the formation of new corpuscles. An increased excretion of pigments derived from the hæmoglobin,—viz., bilirubin and urobilin, is also to a certain extent indicative of an increased destruction of the erythrocytes.

The red blood-corpuscles themselves frequently show changes in anæmia. In the first place, they may be of irregular shape, so that hardly any two look alike (poikilocytosis). Then they may vary greatly in size, some being extremely small, the so-called microcytes, while others are extremely large, the so-called macrocytes. Finally, they may show clear spaces in their protoplasm (endoglobular degenerations). All of these changes are of a degenerative character.[3]

The staining properties of the red blood-corpuscles may also be altered. Normally they stain evenly but somewhat more intensely toward the periphery. In the bone-marrow the very

[2] Stühlen, Arch. f. klin. Med., vol. liv. p. 248.
[3] Weintraud, Virch. Arch., vol. cxxxi. p. 497.

young forms often take up several abnormal tints when stained with certain complex stains; *i.e.,* they are polychromatophilic. It seems probable that degenerating cells may exhibit similar abnormalities in their staining properties. This abnormal affinity for certain pigments may affect the entire cell, or it may be limited to certain granulations.[4] The latter, known as granular basophilia, is particularly well marked in the anæmia of chronic lead poisoning. The old strife as to whether polychromatophilia is a sign of degeneration or of regeneration seems to have given way to the view that it may indicate either; although in time it is possible that we shall learn to recognize differences which will serve to distinguish the two modes of origin.

In certain forms of anæmia the quantity of hæmoglobin is relatively greater than the number of red corpuscles, whereas more commonly it is relatively less. In still other conditions, the corpuscles contain abnormal amounts of water, even though there be no change in the percentage of water in the plasma.

The presence of nucleated red blood-corpuscles in the circulation is usually indicative of an increased formation of these cells. Such nucleated red cells are found normally only in the tissues in which erythrocytes are produced,—viz., the red marrow of the bones and, during fetal life, the liver and spleen. The red cells that pass into the blood normally have already lost their nuclei. When regeneration is very active, however, immature, nucleated, red cells escape into the circulation. (No absolutely strict parallelism exists between the number of nucleated erythrocytes in the peripheral blood and the amount of regeneration in the bone-marrow. On the one hand, as in "aplastic anæmia," nucleated cells may appear in the blood, even though there is a diminished formation of red cells in the marrow; whereas, on the other hand, nucleated cells may be absent from the peripheral circulation for weeks,

[4] Cohn, Munch. med. Wochens., 1900, No. 6.

even though, as in pernicious anæmia, we have every reason to believe that their formation is increased.—ED.) In very severe anæmias we may find nucleated red cells of normal size,—the so-called normoblasts,—together with those of large size,—megaloblasts. The presence of the latter has been regarded by many [5] as an indication that the formation of the red corpuscles has returned to the embryonal type. For reasons which will appear in the discussion of pernicious anæmia, we prefer to regard these cells merely as the prcducts of any exceedingly rapid regeneration of red corpuscles. According to the observations of Engel,[6] furthermore, these megaloblasts have nothing whatever to do with the embryonal red cells.

The red bone-marrow is increased in quantity in many forms of anæmia. Normally this tissue is limited to the flat bones and the extremities of the long bones. If, however, the necessity arises for a greater production of red cells, then the red marrow spreads over many bones, the change being in the nature of a compensatory process. We are among those who believe that all increases of red marrow are of this nature, and that there is no necessity for making a division between normal and pathological red marrow.

Chlorosis.—Certain forms of chronic anæmia are sufficiently well defined to be distinguished clinically. Of these, we shall first consider chlorosis. This occurs usually, perhaps exclusively, in girls at about the time of puberty. Its cause is not well understood. Unsanitary surroundings are certainly not the sole causative agents, for the disease occurs with about equal frequency among the upper as well as the lower classes. Some have ascribed chlorosis to disturbances of the nervous system, others to diseases of the female genitalia, but both, it seems to me, without sufficient evidence.

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[5] Rindfleisch, Virch. Arch., vol. cxxi. p. 176; Ehrlich, Kongr. f. in. Med., 1892, p. 33; H. F. Müller, Arch. f. klin. Med., vol. li. p. 282.

[6] Die klinische Untersuchung des Blutes, Berlin, 1900.

The color of the skin in chlorosis usually varies from a slight pallor to the typical, pale, greenish tint. The face, however, may be of an unusually brilliant color (chlorosis rubra). At times the patient is emaciated, more frequently, however, the fat is well preserved. The nervous symptoms present are for the most part, caused by the anæmia.

The blood always shows a diminution in the quantity of hæmoglobin to the unit-volume, and the individual red corpuscles are usually paler than normal. Many of them are of small size, and some are deformed in shape. In severe cases, nucleated red corpuscles may be present, being either of normal size or very exceptionally of the megaloblastic type.[7] In some cases, the number of red corpuscles is normal, but usually it is moderately diminished. v. Limbeck[8] states that, of two hundred and seventy-nine cases of chlorosis, only one hundred and five, or thirty-seven per cent., showed no diminution in the number of the red corpuscles.

That the amount of hæmoglobin is diminished has been demonstrated by colorometric, spectrophotometric, and chemical methods. The dried blood may show 0.03 per cent. of iron instead of the normal 0.06 per cent.[9] And although these results have been more recently questioned,[10] it does not appear to me that the method of obtaining the red corpuscles was one which is free from objection.[11]

As in other anæmias, the volume of the red cells is also changed.[12] In chlorosis, the leucocytes do not vary greatly from the normal. The percentage of water in the serum is approximately normal in the milder cases, whereas in the more

[7] Hammerschlag, Wien. med. Presse, 1884.

[8] Klin. Path. des Blutes.

[9] Becquerel and Rodier, Unters. ü. d. Zusam. d. Blutes, 1845.

[10] Biernacki, Ztft. f. klin. Med., vol. xxiv. p. 460.

[11] See, also Wendelstadt u. Bleibtreu, Ztft f klin. Med., vol. xxv. p. 363.

[12] Kossler, Zentralbl. f. in. Med., 1897, No. 26.

severe ones it is increased.[13] The total quantity of blood in the body seems considerable.[14] Of other changes in the serum we know little. From the fact that patients with chlorosis show a tendency to the formation of venous thrombi, it has been assumed that their blood contains larger amounts of fibrin ferment, an assumption, however, which is incorrect.[15] Not infrequently there is a retention of water in the body of chlorotic patients, but its cause is not well understood.

Autopsies upon patients with chlorosis are few in number, and these have shown surprisingly little that was abnormal.[16] No degenerative changes were present in the liver, heart, or kidneys, and no changes in the bone-marrow of the tibiæ were found. Virchow observed a general hypoplasia of the heart and blood-vessels, and especially a narrowing of the aorta, and these have been assumed to be causative agents in the production of the disease. This view, however, does not appear very reasonable, for it is difficult to understand how chlorosis could heal as completely as it does if this were its cause; and, furthermore, stenosis of the aorta is known to produce quite a different set of symptoms.

Although chlorosis heals spontaneously in practically every case, the healing is greatly accelerated by the administration of iron. Indeed, proper food seems to be of secondary importance, for chlorosis may develop in individuals who have lived in the best of surroundings. The brilliant results achieved by the administration of iron are in themselves almost characteristic of this type of anæmia, for in no other form do we see such striking effects, save possibly in those anæmias which result from hemorrhages.

The value of the administration of iron in chlorosis lends

[13] See Grawitz, Klin. Path. des Blutes.

[14] v. Jaksch, Ztft. f. klin. Med., vol. xxiii. p. 187; Stintzing u. Gumprecht, Arch. f. klin. Med., vol. liii. p. 265.

[15] Quenstedt, Diss. Tübingen, 1902.

[16] Grawitz, Klin. Path. des Blutes, p. 279.

support to the theory that the cause of the disease is an inadequate or improper formation of the red blood-corpuscles. We possess no evidence favoring the opposite possibility,—viz., that there is a pathological destruction of the red cells, for degenerative changes in the red corpuscles are not marked, jaundice does not occur, and the quantity of pigments in the urine and fæces is less than normal. These facts cannot be regarded as proof that there is no pathological destruction of red cells in chlorosis, but they certainly render it very improbable. Unfortunately, we possess no evidence on the more decisive question as to whether or not there is an excessive deposit of iron pigment in the liver. Nevertheless, from the facts in our possession, we may assume that the underlying cause of chlorosis is an insufficient formation of red blood-corpuscles.

The exact manner in which iron exerts a favorable effect upon chlorosis still remains unsettled. The patients, suffering from this disease, ordinarily show no marked digestive disturbances, although some, at least, seem to absorb fats poorly.[17] There is likewise no conclusive evidence that their absorption of iron from the intestinal tract is less than normal, though the data upon this point are not very accurate. It is therefore difficult to understand why the iron salts in the food, which are sufficient for all ordinary needs, are insufficient in chlorosis. It seems to me most probable that iron cures chlorosis by acting as a stimulant to the blood-forming organs, very much as does arsenic in certain other forms of anæmia.[18]

Secondary Anæmias.—The remaining forms of anæmia are, for the most part, merely symptomatic of other pathological conditions. Where their causation is known, they are termed secondary anæmias, in contradistinction to the so-called primary anæmias, whose causes are unknown. This classifica-

[17] Wallerstein, Diss. Bonn , 1890.
[18] v. Noorden, Berl klin. Wochens., 1895, Nos. 9 and 10; Hofmann, Virch. Arch., vol. cxl. p. 235.

tion into primary and secondary anæmias is serviceable, but hardly final, for it seems certain that, as we become better acquainted with the causation of anæmias, the number of cases assigned to the primary group will progressively diminish and the number classified as secondary anæmias will correspondingly increase.

A great variety of causes may give rise to mild and moderately severe forms of secondary anæmia. Of these, we may first mention repeated hemorrhages, such as may occur from ulcer or from carcinoma of the stomach, from intestinal ulcerations, from hemorrhoids, from uterine myomata, etc. Secondary anæmias may result, furthermore, from chronic poisoning, as by lead or mercury, from gastro-intestinal disease, from malignant tumors, from infections such as tuberculosis, syphilis, and malaria, and from chronic diseases of the liver, kidneys, heart, or nervous system. It should be remembered, however, that none of these diseases necessarily give rise to an anæmia.

It is still uncertain in what manner many of these diseases produce the anæmia. Infectious processes frequently injure the red blood-corpuscles directly, as may be inferred from the degeneration which they produce in these cells. Yet the destruction of a few corpuscles, more or less, would hardly give rise to an anæmia, for considerable numbers would be immediately replaced by regenerative processes. In malaria, the plasmodia certainly destroy the corpuscles in large numbers, and this seems to be the direct cause of the malarial cachexia. In nephritis, the reduction in the number of red cells per unit of volume may be due in part to a dilution of the blood, and in part, as in hemorrhagic nephritis, to repeated losses of blood in the urine.

Insufficient nourishment will give rise to an anæmia in some cases. An absolute fast, even if continued up to death, merely causes a reduction in the total quantity of blood without any diminution in the hæmoglobin or red curpuscles to the

unit of volume. If, after such a fast, food and liquids be taken in sufficient quantity, then water is rapidly added to the blood with a resulting reduction in the percentage of hæmoglobin and in the number of red cells per unit of volume. The prolonged use of food, deficient in some important constituent, will also cause an anæmia. For example, a continuous milk diet will have this effect, on account of the small quantity of iron in the milk. Especially injurious is the combination of improper food and continued hard work. Other favoring factors are care and worry, poor light, poor air, lack of sleep, etc. Patients with anæmia from such causes improve most markedly if their surroundings are improved;[19] and although their absorption of iron may be less than normal,[20] yet the simple administration of salts of this metal without a change in their surroundings has comparatively little effect upon their anæmia.

Finally, mild and moderately severe secondary anæmias of this character may occur in patients who live under the best of hygienic surroundings, and we are unable to form any conception as to their cause. Many such individuals seem to feel perfectly well, so that one might almost question whether their anæmia was physiological or pathological. Others, however, suffer from the same symptoms as do most anæmic patients, these symptoms being especially marked upon exertion.

The blood picture in the secondary anæmias may show considerable variations. In some patients the changes are hardly demonstrable, while in others they may be of the most extreme grade.

Certain possible fallacies in the methods of blood examination should be noted. In the first place, the ordinary examination of the blood may show nothing abnormal, and yet there may be a reduction or an increase in the total quantity of blood

[19] Grawitz, Klin Path. des Blutes, pp. 159-163.
[20] Hösslin, Münch. med. Wochens., 1890, Nos. 38 and 39.

in the body.[21]   On the other hand, it is possible that the blood may be of different constitution in different parts of the body, so that the cutaneous capillaries contain relatively few or relatively many corpuscles.   Such possibilities of error cannot be easily eliminated in our clinical methods of blood examination.

In secondary anæmia the red cells frequently vary in staining properties (polychromatophilia) and in shape (poikilocytosis).   The dimensions of the cells may vary more widely than in health, so that we find microcytes and megalocytes.   Signs of rapid regeneration are also frequently met with, especially nucleated red cells of normal size (normoblasts), and, very rarely, nucleated red cells of large size (megaloblasts).   All these changes are dependent rather upon the severity of the anæmia than upon its cause.   As a rule, the white cells are normal unless some special cause for a leucocytosis is present.   Changes in the blood-serum will be considered in another place.

Pernicious Anæmia.—In the third form of anæmia, the so-called pernicious form, the variation in the red cells reaches its maximum.   Their number is greatly reduced, and Quincke has reported a case in which only one hundred and forty-three thousand per cubic millimetre were counted.   The hæmoglobin is also markedly diminished, although, as a rule, it is relatively less reduced than is the number of the red corpuscles; in other words, the average red corpuscle contains as much or more coloring matter than normal ones do.   Poikilocytosis becomes extreme.   At times, only a small proportion of the red cells present a normal appearance.   The majority show some one or other of the many changes which have already been described.   Nucleated red cells are especially numerous, the most characteristic and often the predominating form being the megaloblasts.   The nuclei of these cells are often found in the process of division.   The leucocytes are only rarely increased; usually their number is normal or is diminished.

[21] Stintzing and Gomprecht, Arch. f. klin. Med., vol. liii. p. 287.

As a rule, in pernicious anæmia, the blood-serum is not particularly deficient in solids.[22] Grawitz found, however, that such a deficit is apt to be marked in those cases of severe anæmia which are due to malignant tumors or to chronic infectious diseases. Indeed, he has shown experimentally that pieces of carcinoma introduced into the circulation of animals will attract lymph and thereby cause a dilution of the blood-plasma. The weight of the total solids of the blood is always markedly diminished, owing to the small number of corpuscles. The total amount of blood in the body also appears to be less than normal, if we may judge from the impressions received at the bedside and at autopsy.

The effects of a very severe anæmia upon the patient are often most striking. His brain and muscles are easily fatigued, he suffers from shortness of breath and from fainting spells; gastric secretion is diminished or entirely absent. There is often a great tendency to bleeding, especially into the skin and retinæ. Fatty degeneration of various organs is the rule, it being especially marked in the liver, the kidneys, and, above all, in the heart muscle. Not infrequently fever is present, due possibly to substances liberated from the disintegrated red blood-corpuscles, but as to this there is still some uncertainty.

Very remarkable changes are found in the central nervous system in pernicious anæmia.[23] The most frequent anatomical lesion is degeneration of the posterior columns of the spinal cord, though the lateral columns and the gray matter may also be diseased.[24] The cause of these changes is still uncertain. Some believe that they are caused by the anæmia, others that they are due independently to toxic influence.

The pernicious form of anæmia must be regarded merely

[22] Hammerschlag, Ztft. f. klin Med , vol xxi. p. 478; Grawitz, Klin. Path. des Blutes, p. 215.

[23] Lichtheim, Kongr. f. in. Med., 1887, p. 84.

[24] Teichmuller, Ztft. f Nervenheilk., vol. viii p 385.

as a symptom-complex which may be caused by a variety of pathological processes. For a certain group of cases no cause has yet been found, and to this group is given the name of essential pernicious anæmia, or the Biermer or Addison type of anæmia. Such cases appear to be especially frequent in certain localities,—e.g., Switzerland.

The blood-picture which we have described was at one time regarded as characteristic of this essential pernicious anæmia of unknown causation; yet time has shown that the same blood-findings may be present in anæmias of known origin. There has been a continual endeavor on the part of certain investigators to differentiate these two forms of pernicious anæmia, and special emphasis has been laid upon the presence of megaloblasts as favoring the diagnosis of the essential pernicious form. Yet megaloblasts have also been found in the secondary forms of pernicious anæmia. Among the diseases which have given rise to a pernicious type of anæmia are syphilis,[25] carcinoma of the stomach, gastric ulcer, ulcerating carcinoma of the uterus, hepatic affections, and diseases of the bone-marrow.[26] Hunter has claimed that the condition may be produced by a chronic intoxication from oral sepsis,[27] yet this view has not received general acceptance.[28] (It has also been claimed that pernicious anæmia is caused by subinfection with intestinal bacteria, and a similar condition has been produced in rabbits by injecting them with sublethal doses of the colon bacillus. Even the spinal cord changes were thus reproduced.[29]—Ed.) Atrophy of the

[25] Müller, Charité-Annalen, vol. xiv. p. 253; Klein, Wien. klin. Wochen., 1891, No. 40.

[26] Literature in Grawitz, p. 231; and in Ewing, Clin. Path. of the Blood, p. 205.

[27] Lancet, 1888, 1889, 1900, 1903.

[28] Bloch, Arch. f. klin. Med., vol. lxxvii. p. 277; McCrae, cit. in Ewing, p. 211.

[29] Charlton, Jour. of Med. Research, vol. xi., No. 2, 1904.

gastro-intestinal mucous membrane is frequently present in pernicious anæmia, but we know that it may also occur without causing the disease. Some believe that repeated small hemorrhages may be a causative factor, although this is denied by others. It is universally agreed, however, that at least two forms of intestinal parasites, bothriocephalus latus and anchylostoma duodenalis, may produce a pernicious type of anæmia. From these numerous observations it has been proved that it is impossible to draw any sharp distinguishing line between those anæmias of a pernicious type that are due to known causes and those that appear to be primary.

In what manner the various causes affect the blood is not always clear. With the possible exception of the anchylostoma duodenale, it seems improbable that losses of blood play any great rôle. In the case of malignant tumors, hæmolytic toxins are possibly responsible for the blood condition.[30] It seems very probable also that this is the case in the anæmia produced by the bothriocephalus latus.[31] Apparently many individuals harboring intestinal parasites become immunized against their poisons, a supposition which would explain the fact that a man may have the parasites in his intestines without manifesting any symptoms, and that periods of improvement and relapse may alternate.

. The prognosis of the pernicious form of anæmia depends mainly upon its cause. In the primary, essential form, the outcome is usually fatal; in the secondary forms, recovery may take place if the cause be discovered and removed, and if the process be not already too far advanced. This is especially true of those cases due to intestinal parasites.

In pernicious anæmia there is unquestionably an increased destruction of the red blood-corpuscles, as is proved especially

[30] Kullmann, Ztft. f. klin. Med., vol. v. p. 3.
[31] Schaumann and Tallquist, Deut. med. Wochenschr., 1898, No. 20; Rosenquist, Ztft. f. klin. Med. vol. xlix. p. 193.

by the abnormal deposits of iron salts in the liver and in other organs. The anæmias caused by losses of blood or of serum, even though most severe, are unaccompanied by such deposits of iron. The pigmentation so frequently found in the spleen, the bone-marrow, the kidneys, and the liver, the not infrequent jaundice,[32] and increase in the coloring-matter of the urine, likewise support the idea that in pernicious anæmia there is an unusual destruction of the red blood-corpuscles.

On the other hand, we have evidence that there is also an increased regeneration of erythrocytes, for the red bone-marrow spreads to parts of the bones from which it is normally absent, and in this red marrow are found erythrocytes of various kinds, but more particularly the large nucleated variety known as the megaloblasts. By the escape of these cells into the blood, one of the most characteristic features of pernicious anæmia is produced.

In pernicious anæmia, therefore, there is both an increased destruction and an increased regeneration of red corpuscles, but we do not know at present which process is primarily at fault. Perhaps the destruction of the erythrocytes is so intense that even the most marked regeneration does not replace the cells destroyed; or perhaps the new cells are so imperfect that they cannot resist the normal wear and tear in the body, and consequently disintegrate with abnormal ease. Some hold that the disease consists essentially in a return to the embryonal type of blood formation.[33] Yet there is no reason to consider that the blood and marrow changes are other than would result from an excessively active regeneration of erythrocytes, with the escape of immature corpuscles into the circulating blood. We do, however, possess direct evidence that the red corpuscles of pernicious anæmia are more vulnerable to injury

[32] Sylleba, Cit. in Folia Hæmatologica, vol. i. p. 283.

[33] Ehrlich, Kongress f. in. Med., 1892, p. 33; Rindfleisch, Virch. Arch., vol. cxxi. p. 176; H. F. Müller, Arch. f. klin. Med., vol. li. p. 282.

than are normal corpuscles, and that they may be destroyed with comparative ease.[34] This seems to be especially true of the malignant anæmia of syphilis.[35]

We know little about the pathological variations in the chemical constitution of the red blood-corpuscles, for the necessary analyses present special difficulties. It is known, however, that in cholera the specific gravity of the red cells is increased, owing to the loss of water, whereas in other conditions they may become swollen from an absorption of water.

Hæmoglobinæmia.—Thus far we have considered the hæmoglobin only as it constitutes a part of the red blood-corpuscles If it escapes from the corpuscles into the plasma, the condition is known as hæmoglobinæmia. Hæmoglobin which has become free in the plasma is quickly removed, principally by the liver, and, to a lesser extent, by the spleen and bone-marrow. If these organs fail to remove it completely, it is excreted in the urine, giving rise to hæmoglobinuria. According to Ponfick,[36] the latter is produced when about one-sixth of the total hæmoglobin of the blood is set free from the cells. The stromata of the cells which have lost their hæmoglobin are deposited in the spleen, and cause a swelling of that organ Since the liver manufactures bile-pigments from hæmoglobin, the bile becomes unusually rich in coloring-matter and the fæces become darker. The hæmoglobin which is removed by the liver and kidneys is naturally lost to the body, but even that which remains dissolved in the plasma is in part rendered useless as an oxygen-carrier by being transformed into methæmoglobin, a compound, isomeric with oxy-hæmoglobin, but differing from it, in that it is unable to give up its oxygen in the tissues.

[34] Pappenheim, Ztft f. klin. Med , vol. xliii. p. 363; Bloch, Arch f. klin. Med , vol. lxxvii. p. 277.

[35] Samberger, Wien klin. Rundschau, 1903, Nos. 43 45.

[36] Virch. Arch , vol lxii p 273, and vol. lxxxviii p 445

Such a passage of the hæmoglobin from the corpuscles into the plasma, or, as it is called, a laking of the blood, may be brought about by several causes. The stromata of the red cells may be directly injured or their osmotic tension may be changed so that they become unable to retain their hæmoglobin; or, on the other hand, a lowering of the osmotic pressure of the plasma may bring about the same result. The latter seems to be of comparatively little importance, for the red cells are normally resistant to considerable changes in the osmotic pressure of the plasma, and considerable amounts of water may be infused into the circulation without causing a laking of the blood.

We have said that the hæmoglobin free in the plasma may become converted in part into methæmoglobin. Certain poisons possess the property of effecting this conversion of the hæmoglobin directly within the red cells. If the injury to these cells be not too severe, it is possible that the methæmoglobin so formed may be transformed back again into oxyhæmoglobin.[37] If the corpuscles are more seriously damaged, however, they disintegrate and their coloring-matter passes into solution.

Three different processes may therefore give rise to hæmoglobinæmia: first, osmotic changes in the plasma; secondly, a primary injury to the red blood-corpuscles; and thirdly, a primary transformation of the oxyhæmoglobin into methæmoglobin. These processes may run courses quite independently of each other, but for the most part, they are combined to some extent, and it is often difficult, in the individual case, to say which was really the primary change.

Of the poisons which will give rise to a laking of the blood, we may name those of the poisonous fungi, the bile salts, arsenuretted hydrogen, and the plasma of alien animals. The

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[37] Dittrich, Arch. f. exp. Path., vol. xxix. p. 247.

toxins produced by micro-organisms may also injure the corpuscles, and hæmoglobinæmia has been observed in severe cases of typhoid fever, scarlet fever, and other infectious processes, it being especially severe in certain forms of tropical malaria (fièvre bilieuse hémoglobinurique). In such cases, the plasma dissolves its own corpuscles. Italian observers [38] have described such a globulicidal action of the plasma in association with a great variety of diseases. Whenever the destruction of the corpuscles exceeds a certain limit, hæmoglobinæmia and, ultimately, hæmoglobinuria occur.

The Hæmolytic Action of Alien Plasmas.—The whole subject of the destruction of red blood-corpuscles, especially by alien blood, has in recent years become a matter of very great interest on account of the broad biological principles involved. It has long been known that the blood of certain animals has the property of destroying the corpuscles of other animals. For this reason the transfusion of blood from one animal into another has failed of any practical application. The red blood-corpuscles of certain animals are peculiarly susceptible to such changes of environment, while the sera of others are especially poisonous. A schematic arrangement of the bloods of various animals according to these properties is, however, hardly possible on account of the great individual variations. The serum of an animal may even dissolve the red blood-corpuscles of another individual of the same species.[39] According to some writers, the hæmolysis is due to the different osmotic properties of the foreign serum; but at present, most investigators believe that the hæmolysis is produced by certain chemical substances in the foreign serum, which have been designated by Buchner and by the French school as alexins, by Ehrlich and his pupils as complements (addiments).

[38] Maragliano, Kongr. f. in. Med., 1892, p. 152; Maragliano and Castellino, Ztft. f. klin. Med., vol. xxi. p. 415.

[39] Ehrlich and Morgenroth, Berl. klin. Wochenschr., 1900, No. 21.

These alexins are destroyed if they are heated to a temperature of about 56° C. for half an hour.

It is possible to increase the hæmolytic action of a serum enormously. If the red corpuscles of an animal A, be injected into an animal B, then the serum of B usually acquires the property of destroying the corpuscles of A, even though it had not possessed this property previously, and if it had had the property before, its hæmolytic power may be increased many times by this treatment. The same results are obtained if, instead of the entire red corpuscles, the stromata alone are used This process is spoken of as an immunization of one animal against the red blood-corpuscles of another; and it is analogous to a form of immunity which follows similar injections of bacteria into the animal body (bactericidal immunity).

To what substances does the serum owe its increased hæmolytic activity? Let us describe the classical experiment of Bordet. The blood-serum of a normal rabbit does not dissolve the red blood corpuscles of the guinea-pig; yet several intraperitoneal injections of guinea-pig's blood confer upon the rabbit's serum the property of dissolving the guinea-pig's erythrocytes with great rapidity. This property is, however, lost if the immunized rabbit's serum be heated to 56° C. for half an hour. Yet this serum, thus inactivated by heat, regains its activity if fresh normal rabbit's serum, itself inactive, be added to it. Two substances, therefore, must take part in an hæmolysis of this character: the one is contained in normal serum and is destroyed by a temperature of 56° C.; the other is formed in the process of immunization and is resistant to such a temperature. The former is the alexin of which we have already spoken. The latter, the so-called immune body, is specific for the kind of blood injected. There is a great affinity between it and the corresponding corpuscles, so that if the inactivated serum and the foreign red corpuscles be

mixed and allowed to stand, and if then the red cells be separated by centrifugalization, they will carry the immune body out of the serum with them, and they are then susceptible to the action of fresh normal serum which would otherwise be without effect upon them.

It cannot be doubted that the hæmolysis induced by immune sera is due to the action of these two substances. All are not yet agreed, however, as to whether the hæmolysis produced by the action of normal sera is likewise due to two substances or is due only to one. Personally, I believe that the former supposition is supported by the better evidence. Thus the inactivated serum of a dog will not dissolve the red blood corpuscles of the guinea-pig, but it is able to do so if fresh guinea-pig's serum be added, although the latter alone is naturally without any action upon its own corpuscles. It is difficult to explain this fact other than by supposing that there are two substances involved in the process, the immune body being contained in the dog's serum, the complement in that of the guinea-pig.

Ehrlich has brought forward a great array of facts in support of the view that there are in normal, as well as in immune, sera a great variety of immune bodies and of complements. The question is one of considerable importance in bacteriology and the theory of immunity, and will be considered in another place.

Paroxysmal Hæmoglobinuria.—The condition known as paroxysmal hæmoglobinuria is characterised by the passage of red to dark-brown urine. Like other varieties of the more usual forms of disease, or to characterise other, is due to the presence of hæmoglobin in the urine, given with low of any red blood-corpuscles in the typical cases. The paroxysm is usually accompanied by chills, fever, and pains in various parts of the body. In a case the liver and spleen become enlarged and produce very severe. This

a few hours or days, the symptoms disappear, and only the dark-colored faeces remain as evidence of the paroxysm which has just ceased.

Malaria and syphilis appear to be predisposing causes of this disease. In some individuals the attack is precipitated by muscular exertion, in others by exposure to cold. Indeed, some patients void the characteristic urine whenever they are exposed to a low temperature, or even when a single hand is dipped into ice-water. During the intervals between the paroxysms, the patient may appear to be perfectly well, or he may continue to show albumin in the urine. Ralfe[40] has reported the case of a man who had cyclic albuminuria in conjunction with paroxysmal haemoglobinuria, and a similar case has been observed by the author.

A haemoglobinaemia probably antedates, in all cases, the appearance of the blood-pigments in the urine. In these patients, the red blood-corpuscles appear to be less resistant than normal, so that they more readily succumb to unfavorable influences. The nature of these unfavorable influences has been a matter of dispute. Some have held that the cold itself is the destructive agent, but careful direct observations have failed to confirm this view. The red corpuscles of these individuals are no more readily destroyed by cold than are those of normal persons.[41] Chvostek believes that the cold causes a stasis of the blood in the internal organs, and that this leads to the destruction of the red cells; yet it is difficult to see why there should be any stasis of blood in the internal organs, and the question remains *sub judice*. Undoubtedly vasomotor phenomena, induced by cold, initiate many of the paroxysms, and quite probably the red blood-corpuscles are destroyed because they possess less resistance than normal

[40] Lancet, 1886, p. 764.

[41] Ehrlich, Charité-Annalen, vol. x. p. 142; Chvostek, Ueber das Wesen der paroxysmal Hæmoglobinuria, Leipzig, 1894.

cells.[42] It is possible that the circulatory disturbances are in some way directly responsible for the destruction of the red corpuscles.

The large quantity of blood-pigment liberated from the corpuscles is partially taken up by the liver, the disintegrated stromata are deposited in the spleen, and both of these organs become enlarged. The hæmoglobin that remains in the plasma is excreted by the kidneys, and seems to injure them, for a certain amount of albumin likewise passes through into the urine. The hæmoglobin taken up by the liver is mostly converted into the bile-pigments, and for this reason the stools become dark. The fever, anxiety, and occasional dilatation of the heart may quite possibly be due to the toxic properties of substances resulting from the disintegration of the stromata of the affected corpuscles.[43]

Other Causes which injure the Red Blood-Corpuscles.— Extensive superficial burns may cause the red corpuscles to break up into smaller particles, and lead to a liberation of hæmoglobin in the plasma, not only from these disintegrated corpuscles but from others, which, microscopically at least, appear to be normal.[44] The hæmoglobin, dissolved in the plasma, is taken up by the liver and kidneys, partly as methæmoglobin, and the urine consequently contains both these pigments. The cellular residues are taken up especially by the spleen and bone-marrow, and, to a lesser extent, by other organs. They produce symptoms which will be described later.

Many poisons are able to convert the hæmoglobin of the red blood-corpuscles into methæmoglobin, among the more important of which are potassium chlorate, acetanilide, and

[42] Kretz, Wien. klin. Wochenschr., 1903, No. 18; Donath, Ztft. f. klin. Med., vol. lii. p. 1.

[43] Stadelmann, Der Ikterus, Stuttgart, 1891.

[44] Silbermann, Virch Arch., vol cxix. p. 488; Wilms, Mitth. a. d. Grenzgeb., vol. viii. p. 393.

other coal-tar products.[45] The first does not exert the same action upon the blood of all species of animals, for the corpuscles of some appear to be especially resistant to the action of this poison.[46] Even in the same individual, accessory causes may render the corpuscles more or less vulnerable to the action of potassium chlorate. Thus Mering [47] has shown that the red cells are rendered susceptible by fever or by a reduction in the normal alkalinity of the blood, produced by the administration of mineral acids. The toxic effects from the administration of potassium chlorate appear, therefore, to depend upon two factors,—first, upon the amount of the salt in the blood at a given time; and secondly, upon the resistance possessed by the red corpuscles.

Systemic Effects resulting from the Rapid Destruction of Red Blood-Corpuscles.—The effects of such intoxications upon the body as a whole depend partly upon the loss of functioning hæmoglobin and partly upon the toxic substances derived from the destroyed corpuscles. In very severe intoxications with potassium chlorate, death results from the diminution in the respiratory capacity of the blood, caused by the loss of hæmoglobin.

The destruction of a large number of red corpuscles sets free in the plasma certain substances, apparently enzymes, which tend to produce intravascular clotting. A limited quantity of such substances may be neutralized or destroyed by the living organism; but when they appear in very large amounts, they give rise to thrombi in the smaller blood-vessels. As results of such thrombi, we find necroses in various tissues, and the gravity of the intoxication often depends upon the localities in which the coagula form.

[45] Marchand, Arch. f. exp. Path., vol. xxii. pp. 23, 201, 273, 347; F. Müller, Deut. med. Wochens., 1887, No. 2.

[46] v. Limbeck, Arch. f. exp. Path., vol. xxvi. p. 39.

[47] Mering, Das chlorsaure Kali, Berlin, 1885.

The fact that there is a slow coagulation of the blood in certain cases of extensive burns in no way excludes the possibility that thrombi have formed, for we know that the presence of substances in the blood which favor coagulation may in turn give rise to substances having the very opposite effect, so that ultimately the coagulation will be retarded. Opinions differ as to the rôle played by these thrombi in the above-mentioned intoxications and burns. Some observers have found them in the majority of cases,[48] while others have missed them with equal frequency.[49]

The large quantities of hæmoglobin or methæmoglobin which may pass into the urine in these conditions seem to injure the kidneys directly, and not infrequently the urine contains large amounts of albumin, numerous blood and epithelial cells, and a great variety of casts, the most characteristic of which are composed of clumps of blood-pigment. The quantity of urine may diminish up to complete anuria, and the patient may die of uræmia. The danger from renal complications persists for some time after the original cause of the hæmoglobinæmia has disappeared.

THE WHITE BLOOD-CORPUSCLES.

The white blood-corpuscles may be divided into groups according to their size, the character of their nuclei, and the staining reactions of their protoplasm. About seventy per cent. are made up of cells that are slightly larger than red corpuscles, and that contain irregular nuclei and protoplasmic granules, staining with neutral aniline stains. From twenty-five to twenty-eight per cent. are made up of mononuclear cells, from two to four per cent. of which are quite

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[48] Silbermann, Virch. Arch., vol. cxvii. p. 228, and vol. cxix. p. 488; Welti, Zieg. Beiträg., vol. iv. p. 519.

[49] Falkenberg, Diss. Marburg, 1890; Wilms, Grenzgeb., vol. viii. p. 393; Bardeen, Johns Hopkins Hosp. Reports, vol. vii.

large, whereas the remainder are about the size of red blood-corpuscles. In addition to these cells, there are from one to four per cent. of eosinophiles, characterized by the presence of large acid-staining granules in their protoplasm, and from 0.5 to two per cent. of cells containing large irregular basic granules (the mast-cells).

The origin of the various forms of leucocytes is still unsettled. According to Ehrlich's well-known views, the small mononuclear forms are derived from the lymphoid tissues of the body, while the polymorphonuclear neurophilic leucocytes are derived from certain large mononuclear cells in the bone-marrow. We hold, however, with those who believe that no such sharp distinction can be made between these two varieties of cells.[50]

Physiological Leucocytoses.—The number of leucocytes in a cubic millimetre of blood is normally about eight thousand. Children have, on the average, somewhat more,—about nine thousand; weak and poorly nourished persons, somewhat less. The number of leucocytes in the peripheral blood varies even in the same individual at different times. Thus it is usually increased after a meal, especially when the meal consists largely of proteid material.[51] Such a " digestion leucocytosis" is absent in some individuals normally, but it is especially apt to be absent in certain diseases, above all in carcinoma of the stomach. During pregnancy, more particularly in the later months, the number of leucocytes is increased. A leucocytosis is also physiological in the new-born. Cold baths and exercise likewise increase the number of leucocytes in the peripheral blood.[52] Some regard this latter as an effect of the

[50] Grawitz, Path. des Blutes; Löwit, Kongress f. in. Med., 1899; Pappenheim, Virch. Arch., vol. clvii. p. 54; vol. clix. p. 40; vol. clxiv. p. 374.

[51] Pohl, Arch. f. exp. Path., vol. xxv. p. 31.

[52] Schulz, Arch. f. klin. Med., vol. li. p. 249; Thayer, Johns Hopkins Hosp. Bull., April, 1893.

more rapid blood-current which tears the leucocytes away from the vessel walls of the internal organs and throws them into the general circulation, and especially into the peripheral capillaries from which the samples of blood are taken.

The conditions which we have just been describing have been termed physiological leucocytoses. The increase in the number of white cells does not usually exceed thirty per cent. of the normal, although in children the number may be doubled. The proportion between the mononuclear and the polynuclear cells remains unchanged in this form of leucocytosis. Since the counts are made from the blood of the peripheral capillaries, the question arises, Is there an actual increase in the total number of leucocytes in the blood, or is there merely a redistribution of the cells, more going to the periphery and fewer remaining in the interior of the body? Studies on animals have shown that there is normally a greater number of leucocytes at the periphery than in the internal organs, but that during the digestion leucocytosis, at least, the number in both places is increased.[53] The new cells are probably derived from the lymph and from the various organs of the body, for no signs of an active regeneration of these cells are to be found. The digestion leucocytosis appears to be due to the presence of substances in the blood which attract the leucocytes. Such substances appear to be present in largest amounts after the ingestion of proteid food, but not all varieties of proteid food exert the same influence. Indeed, it is uncertain just which products of digestion are responsible for the normal digestion leucocytosis. Possibly this leucocytosis indicates a transportation of proteid material from the intestines to other parts of the body.

A hyperleucocytosis is frequently but not always preceded by a hypoleucocytosis. Löwit [54] interpreted this as a primary

[53] Goldscheider and Jacob, Ztft. f. klin. Med., vol. xxv. p. 403.
[54] Studien z Physiol des Blutes, etc, Jena, 1892

destruction of the white corpuscles which precedes a regeneration. Goldscheider and Jacob[55] and others,[56] on the other hand, failed to find any sign of destruction, and believe that this hypoleucocytosis is caused by a massing of the leucocytes in the capillaries of the lungs. More work is necessary to decide this question.

Pathological Leucocytoses.—Many infections cause an increase in the number of white blood-corpuscles in the peripheral blood, the so-called pathological leucocytosis. Although the same varieties of leucocytes are present as in health, the relative proportions are usually changed. In the more common form of pathological leucocytosis, the percentage of lymphocytes is diminished, whereas that of the polymorphonuclear neutrophiles is increased, from eighty-eight to ninety-five per cent. of the latter being frequently found, in contrast to the normal of seventy to eighty per cent.

In other forms of pathological leucocytosis, the relative number of the lymphocytes is increased,[57] such a blood-picture being presented by many cases of pertussis. Of especial interest would be the investigation of the blood-changes in those diseases which give rise to exudates rich in lymphocytes, such as tuberculous meningitis, pleurisy, etc. (Such cases have been investigated by Fauconnet, who failed to find a lymphocytosis in most cases.[58]—ED.)

Still another form of leucocytosis is characterized by the relative increase in the eosinophilic white blood-corpuscles. This has been observed in bronchial asthma, trichinosis, and a variety of other diseases.

Pathological leucocytosis of the first type occurs especially as the result of inflammatory processes and, above all, in

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[55] Loc. cit.

[56] Ewing, New York Med. Jour., March 2, 1895.

[57] Minkowski, Kongr. f. in. Med., 1899, p. 179; H. Strauss, Charité-Annalen, vol. xxiii.

[58] Arch. f. klin. Med., vol. lxxxii., Nos. 1 and 2.

association with those which are accompanied by a purulent exudation, although exudation is not a necessary concomitant. In certain infectious diseases—*e.g.*, typhoid fever, malaria, and uncomplicated tuberculosis—there is usually no increase in the number of white blood-corpuscles in the circulating blood.

The infectious leucocytoses are probably caused either by the secretions of the living bacteria or by the disintegrated bodies of dead ones. Experimentally, it has been shown that various constituents of the bacterial cell may exert an attractive influence upon the leucocytes (positive chemotaxis). Many other substances also appear to exert such a chemotactic influence, and the same substance may, under one set of circumstances, attract the leucocytes, and under another, repel them. The origin of the extra leucocytes has not yet been definitely settled, and we do not know whether they are derived from the bone-marrow, the lymph-glands, or possibly from other tissues.

Whether or not a pathological leucocytosis is of advantage to the individual suffering from an infectious disease is a matter of great importance. Evidence is constantly being accumulated in support of the view that the increased number of leucocytes is beneficial, and assists the organism in warding off the dangers of the infection.[59] The importance of the subject certainly merits further study.

Leucocytoses of the neutrophilic type may also result from hemorrhage and from malignant cachexias. The latter, however, do not always cause an increase in the number of leucocytes in the peripheral blood, and we do not know what is the determining factor in the individual case. Grawitz[60] found that after injecting carcinomatous material into an animal's blood, the latter became more dilute and the number of leuco-

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[59] Jakob, Kongress f. in. Med., 1897, p. 395.
[60] Deut. med. Wochenschr , 1893, No. 51.

cytes was frequently increased. These changes were believed to result from an increased flow of lymph into the blood, and possibly such an increased flow of lymph is the explanation not only of these leucocytoses due to malignant disease, but of those others which follow acute hemorrhage. (If this explanation were correct, we should expect to find a relative lymphocytosis, yet such is not found.—ED.)

Leucocytoses, in which the eosinophilic cells are increased, occur in a variety of diseases, of which we may mention bronchial asthma, various cutaneous lesions, trichinosis, and infections with intestinal parasites. It is interesting that in most of these diseases there exists a local collection of eosinophilic cells at the main seat of the disease; for example, in the bronchi and in the exudate of bronchial asthma, in the lesions of certain skin affections,[61] and about the embryos in trichinosis.[62]

The number of white cells in the blood in pathological leucocytoses usually ranges between ten thousand and thirty thousand per cubic millimetre, but the number may reach one hundred and sixty-eight thousand (Grawitz).

Leucopenia.—A diminution in the number of leucocytes in the peripheral blood, a leucopenia, occurs in a variety of diseases. It has been observed in cachexias, intoxications, many anæmias, and in some infectious diseases, notably in typhoid fever and malaria.[63]

In such leucopenias, the proportion between the numbers of the various kinds of white cells is usually changed. For example, in typhoid fever there is a relative increase in the number of lymphocytes. The cause of these leucopenias is unknown. Possibly they are due to a negative chemotaxis, or

[61] Bettmann, Münch. med. Wochenschr., 1898, No. 39.

[62] Brown, Jour. of Exp. Med., May, 1898.

[63] Thayer, Johns Hopkins Hosp. Reports, vol. iv., No. 1; Billings, Johns Hopkins Hosp. Bull., October, 1894.

possibly to some lesion of the sites of origin of the leuco-
cytes.

Leukæmia and Pseudoleukæmia.—The disease pseudo-
leukæmia, or Hodgkin's disease, is characterized by an en-
largement of the lymph-glands and by an increase of the
lymphatic tissues throughout the body. Clinically it is some-
times difficult to distinguish this disease, on the one hand,
'from generalized glandular tuberculosis, and, on the other,
from lymphosarcoma. Anatomical investigations have shown,
however, that the three diseases are quite distinct.[64]

The number of leucocytes in the peripheral circulation in
pseudoleukæmia is usually either normal or subnormal, but,
as a rule, an increase in the relative number of the mononuclear
forms is present. Although these blood-findings do not differ
essentially from those of glandular tuberculosis, they serve
to establish a fairly sharp line between pseudoleukæmia and
typical lymphatic leukæmia.

The true leukæmias are characterized by an enormous in-
crease in the number of leucocytes and by characteristic
changes in the forms and relative numbers of those present.
The number of white cells in the blood varies from fifty
thousand to two hundred thousand per cubic millimetre in
cases of moderate severity. Even one million and over have
been observed in the peripheral circulation, but it is doubtful
if in these patients the number throughout the body is pro-
portionately high.

Several forms of leukæmia are recognized, the division
being based upon the changes in blood-forming organs and the
varieties of cells in the blood. In the first place, we have mye-
logenous leukæmia, which is characterized by the presence of
large numbers of so-called neutrophilic myelocytes, which

[64] Reed, Johns Hopkins Hosp. Reports, vol. x., Nos. 3–5; Longcope,
Bull. of the Ayer Clin. Lab., No. 1; Simmons, Jour. of Med. Research,
vol. ix.

usually make up from twenty to sixty per cent. of the total number of leucocytes. These myelocytes are large mononuclear cells, containing neutrophilic protoplasmic granules. They are not in themselves absolutely pathognomonic of myelogenous leukæmia, for they may be found in small numbers in other conditions, such as infectious diseases and severe anæmias; yet here their number never reaches the proportion which is characteristic of myelogenous leukæmia. (In bone-tumors, however, from four to seventeen per cent. of myelocytes may be found.[65]—Ed.)

The second form of leukæmia is characterized by an enormous increase in the number of the small mononuclear leucocytes, which usually make up from eighty to ninety-eight per cent. of all the white blood-corpuscles.

In either of these forms of leukæmia, the total number of leucocytes may be reduced by various causes, among which may be named acute septic infections, pneumonia, tuberculosis, etc. (Similar reductions have followed exposures to the action of the X-ray.[66] In some instances, these reductions in the total number of leucocytes have not materially affected the differential count, characteristic of the form of leukæmia under consideration; so that the latter would still enable one to suspect the true condition. In other instances the blood has become, to all appearances, absolutely normal. Nevertheless it is very doubtful if these reductions are anything more than remissions in the course of the disease, for sooner or later, in most cases, a relapse has occurred.—Ed.)

A third form of leukæmia has been described, the so-called acute leukæmia. Typical cases of this form are characterized by the presence in the blood of numerous, large, mononuclear, non-granular cells, which have been regarded by some authors

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[65] Kurpjuwert, Centr. f. in. Med., 1904, No. 15.

[66] Dock, Am. Med., December 24, 1904; Schirmer, Zentralbl. f. Grenzgeb, vol. vii., No. 1.

as large lymphocytes.[87]   Leukæmia running an acute course may, however, present the blood-picture of myelogenous leukæmia,[68] and some incline to regard the large mononuclear cells above described as myelocytes without neutrophilic granulations.[69]

Most patients with leukæmia show an associated anæmia. Poikilocytosis may be present, and in no other condition do we see nucleated red cells in such numbers as in some cases of leukæmia.   These changes in the red blood-corpuscles depend upon alterations in the bone-marrow, which are probably present in every case of leukæmia.

The blood-serum in leukæmia sometimes contains proteids not normally present.   Neucleo-albumins and deutero-albumoses have been found,[70] but at present the meaning of these findings is not clear.   Charcot-Leyden crystals have been found in lymphatic leukæmia in the blood as well as in the fluids of the spleen.   These crystals appear to bear some relation to the presence of eosinophilic cells.

Leukæmia is a disease of middle life, but it may occur in the aged as well as in the very young.   It leads, almost without exception, to a fatal termination.   At autopsy the bone-marrow is found to have lost its ordinary fatty character, and to consist of reddish or grayish tissue.   Histologically this consists mainly of the varieties of cells found in the circulating blood, or of their progenitors.   Thus in lymphatic leukæmia, the mononuclear cells in the marrow are enormously increased, whereas in myelogenous leukæmia, the increase is principally in the myelocytes.   In the later stages of leukæmia, changes in the marrow develop which indicate

[67] Fraenkel, Deut. med. Wochens., 1895, p. 639.

[68] Billings and Capp, Am Jour of the Med Sci , September, 1903

[69] Askanazy, Virch Arch., vol. cxxxvii. p 1; Ewing, Clin. Path of the Blood, 1903, p. 245

[70] Matthes, Berl. klin Wochens., 1894, Nos. 23, 24; Erben, Ztft. f. Heilk., vol xxiv.; Schrumm, Hofmeister's Beitr., vol. iv. p. 442

a rapid multiplication of those cells which give rise to the red blood-corpuscles, and correspondingly the number of nucleated red cells in the circulating blood is increased.

The liver and spleen are enlarged, partly because of the accumulation of leucocytes in these organs, and partly because, in lymphatic leukæmia at least, there is a proliferation of the lymphoid cells *in situ*. In various other parts of the body, leukæmic deposits may also occur, probably owing to a primary formation of white cell thrombi with secondary multiplication of the cells so deposited.

Most leukæmias run a chronic course. The acute form is characterized clinically by fever, hemorrhages, and a rapidly fatal outcome, thus presenting the picture of an acute infectious disease. As we have already said, the blood in many cases, but not in all, is quite characteristic.[71] In chronic leukæmia, hemorrhages and fever may also occur, but they are relatively less frequent. Both symptoms are of interest, for it is possible that they are caused by a destruction of blood-corpuscles. Fever may also occur in pseudoleukæmia, and at times it assumes a characteristic relapsing character, with periods of apyrexia.[72]

The chief feature differentiating pseudoleukæmia from the ordinary type of leukæmias is the number of leucocytes in the unit-volume of blood. The former begins in the lymphatic glands, whereas in the latter the bone-marrow is constantly, and perhaps primarily, affected. A conversion of a pseudoleukæmia into a true lymphatic leukæmia is very rare, although a few such cases have been reported. In one of these,[73] a rupture of the hyperplastic tissue of a pseudoleukæmic gland

[71] Hamman, Am. Med., vol. viii. p. 138.

[72] Pel, Berl. klin. Wochenschr., 1885, No. 1, and 1887, No. 35; Ebstein, Berl. klin. Wochenschr., 1887, Nos. 31 and 45; Westphal, Arch. f. klin. Med., vol. li. p. 103.

[73] Claus, Ueber das maligne Lymphom. Diss., Marburg, 1888.

into a vein could be directly demonstrated, and coincidently a lymphatic leukæmia developed.

The abnormal leukæmic cells may reach the blood either by being passively washed into it, or by their active amœboid movements. Ehrlich has maintained that the former occurs in the lymphatic form of the disease and the latter in the myelogenous form. With our present knowledge, however, it seems impossible to maintain this distinction.[74]

What relation do the changes in the spleen, the bone-marrow, and the lymphatic apparatus bear to each other, and what relation do they bear to the diseases under consideration? In every case of leukæmia, probably, the bone-marrow is more or less affected, although the changes may be only micro-scopical,[75] and in some instances it is the only tissue which presents important pathological alterations.[76] It seems quite certain that the bone-marrow is always primarily affected in myelogenous leukæmia, whereas the lymphatic tissues of the body are primarily affected in lymphatic leukæmia and in pseudoleukæmia. In lymphatic leukæmia the lymphatic tissues of the lymph-glands, the spleen, the intestine, or of the bone-marrow are increased. Whether the lymphocytes present in the blood originate solely from the bone-marrow,[77] or whether they originate from the various collections of lymphoid cells throughout the body, is not yet definitely known. It is, how-ever, of considerable interest that instances of lymphatic leu-kæmia without enlargement of the lymph-glands have been reported.[78] Such cases demonstrate how careful we must be

[74] Löwit, Kongr. f. in. Med , 1889, p. 139.

[75] Dennig, Münch. med. Wochenschr., 1901, No. 4; Blumer and Gordi-nier, Medical News, 1903.

[76] Littem, Berl. klin. Wochenschr., 1877, Nos. 19, 20; Litten, Kongr. f. in. Med , 1892, p. 159.

[77] Pappenheim, Ztft. f. klin. Med., vol. xxxix p 171; in opposition, see Rosenfeld, Ztft. f. klin. Med , vol. xlii. p. 117.

[78] Pappenheim, loc. cit ; Blumer and Gordinier, loc. cit

not to assume that lymphatic leukæmia is essentially a disease of the lymphatic glands. It seems more probable, indeed, that it is primarily a disease of the lymphoid tissue of the bone-marrow, though recent work has shown that numerous mitoses may be present in other organs,[79] and it is quite possible that white corpuscles may arise in tissues which normally produced these cells only during embryonal life, as, for example, in the liver.

In regard to the nature of the pathological process in leukæmia, we wish again to recall the observation from Marchand's laboratory on a case of lymphatic leukæmia which apparently originated from the rupture of a hyperplastic lymphatic gland into a vein.[80] Many facts favor the view that a growth of cells into the blood-stream is the cause of the blood-changes in leukæmia. Thus, as illustrated, pseudo-leukæmia may change into a true leukæmia by the rupture of a hyperplastic gland into the circulation. The hyperplasias of the lymphoid and myeloid tissues are regarded by some authors as analogies of tumors,[81] and when this tumor tissue escapes into the blood-current leukæmia results. Since the conditions in the bone-marrow especially favor such a rupture into the blood-stream, pathological changes in this tissue are most apt to give rise to leukæmia.

("**Aleukæmic Leukæmia.**"—Within recent years evidence has accumulated which demonstrates that we cannot rely entirely upon the blood-findings in making a diagnosis of leukæmia, but that the pathological changes in the tissues is of even greater importance. We have already stated that under

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[79] Askanazy, Virch. Arch., vol. cxxxvii. p. 1; Gumprecht, Arch. f. klin. Med., vol. lvii. p. 523; H. F. Müller, Zentralbl f. Path., vol. v. pp. 553, 601; etc.

[80] Claus, loc. cit.

[81] Pappenheim, Ztft. f. klin. Med., vol. lii. p. 285; Banti, Ztrbl. f. Path., vol. xv. p. 1; Sternberg, Verhandl. d. path. Gesellsch., 1903, p. 30; Warthin, Trans. Assoc. of Am. Physicians, 1904.

the influence of acute infectious diseases, X-ray treatment, etc., the characteristic blood-picture of leukæmia may become modified so that it is absolutely impossible to detect any alterations in the blood; yet, from the fact that these cases usually again relapse, we may infer that the disease has not disappeared. Certain cases of profound anæmia, with no absolute increase, or even with a diminution in the total number of the leucocytes, have shown at autopsy the characteristic qualitative changes of a lymphatic leukæmia. From the pathological picture presented, these must be regarded as instances of leukæmia, in which characteristic leukæmic changes did not appear in the blood; i.e., they are aleukæmic leukæmias.[82]

The pathological picture presented by these cases differs entirely from that described by Reed and others as characteristic of Hodgkin's disease, and the recognition of this masked form of leukæmia throws very grave doubt upon the reported cases in which Hodgkin's disease was believed to have become converted into leukæmia. It seems very probable that all these were instances of leukæmia in which the blood-changes were first absent and later present. It is difficult to see how the glands of Hodgkin's disease should become leukæmic, for they possess none of the ordinary microscopical characteristics of leukæmia. It is doubtful if Hodgkin's disease can be distinguished from aleukæmic leukæmia without microscopical examination of the lymphatic glands, though possibly a relative increase in the mononuclear leucocytes of the blood will prove to be characteristic of aleukæmic lymphatic leukæmia.—ED.)

The theory that leukæmia is due, not to an excessive production, but to a diminished destruction of the leucocytes, deserves to be considered merely to be condemned, for it has been proved that the destruction of these cells, far from being decreased, is actually increased. Many leucocytes may be seen

[82] Blumer, Albany Med. Annals, April, 1905

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in blood-preparations in various stages of degeneration, and the increased elimination of uric acid and of the xanthin bases through the urine indicates an increased destruction of the nucleo-proteids of the body, which are derived, in all probability, from the nuclei of the leucocytes.

The final cause of leukæmia is still unknown. Löwit believes that it is due to an infection with sporozoa, and he has described a separate parasite for each form of leukæmia.[83] Yet his view has not received general acceptance.[84]

PLASMA AND SERUM. THE TOTAL QUALITY OF BLOOD.

Little is known about pure plasma, principally because it is so difficult to preserve it without coagulation. The serum, resulting from coagulation, differs from the plasma within the blood-vessels, in that it contains no fibrinogen, but does contain fibringlobulin and the fibrin ferment. Probably other changes, at present but little understood, also take place in the proteids of the blood during coagulation.

The Quantity of Fibrin.—When normal blood coagulates, about 0.1 to 0.4 per cent. of its weight separates as fibrin. This may be pathologically increased up to one to 1.3 per cent., an increase which is seen especially in diseases accompanied by inflammatory exudations, such as pneumonia, pleurisy, and acute articular rheumatism. In other conditions, the yield of fibrin is less than 0.1 per cent., notably in the anæmias, typhoid fever, and septicæmia. There exists a certain parallelism between the number of leucocytes and the amount of fibrin present in the blood, but the parallelism is by no means a strict one.[85]

Our knowledge of the physiology of blood-coagulation is still so limited that it would be hazardous to speculate on the

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[83] Kongr. f. in. Med., 1900, p. 322.
[84] Türk, Kongr. f. in Med., 1900, p. 251.
[85] Moll, Wien. klin. Wochens., 1903, No. 44.

significance of pathological variations in the amount of fibrin in the blood and the effect that these variations have upon coagulation. It has been assumed that if the amount of fibrin be diminished, the blood will coagulate slowly and there will be a tendency to hemorrhages, whereas, if the amount be increased, coagulation will be rapid and there will be a tendency to thrombosis. These assumptions, however, are not sufficiently supported by facts.

The Blood-Serum.—All substances formed in the metabolic processes within the body and all food-stuffs introduced from without pass through the blood; although they may be present there only in minute traces, because they are so quickly removed by the various organs. It would be impossible to discuss in this place all those conditions in which some constituent or other of the serum is changed, as happens, for example, in diabetes, and it seems better to reserve such a discussion for the chapters on metabolic disorders.

One substance, however, may be mentioned in this connection,—viz., fat. Fatty substances are constantly present in the blood,[86] the amount being increased during the digestion of meals containing much fat. Under pathological conditions, the quantity of fat in the blood may become so great that particles can be recognized microscopically between the red corpuscles, especially if they have been stained by osmic acid.[87] This condition, known as lipæmia, is relatively uncommon. It occurs in various pathological conditions, especially in diabetes, and is frequently merely transitory.

In discussing the chemistry of the blood-serum, we shall consider especially the proportions of proteids, salts, and water. According to Hammarsten's analyses, 9.2 per cent. of the serum consists of solids, of which 7.6 per cent. are proteids. Since the proteids form the greater part of the

[86] Rumpf, Virch. Arch., vol. clxxiv. p. 163.
[87] Gumprecht, Deut. med. Wochenschr, 1894, No. 39.

solid material in the serum, they and the water ordinarily vary in inverse ratio to each other, a high percentage of proteids being accompanied by a relatively low percentage of water, and *vice versa*.

The proteids of the serum consist chemically of albumin and various forms of globulin.[88] Recent biological work, however, has shown such a variety in the proteids of the blood that we can no longer regard the above simple chemical division as in any way a final one; and when we remember that in all probability each organ contributes its quota to the blood, it seems impossible that the division into albumin and globulins could be any other than a mere classification of the proteids present under these group names. The serum of healthy men contains somewhat more albumin than globulin, the ratio being about 4.5 to 3.1. This ratio differs in different species of animals, and varies in the same individual under different circumstances. The earlier idea that the albumin diminishes during fasting has not been confirmed by later and more accurate work.[89]

The total quantity of proteids in the serum may be determined either by precipitation methods or by determinations of the total amount of nitrogen present. The latter method is applicable only when we can be certain that there is no retention of nitrogenous by-products in the blood, the quantity of these substances, ordinarily present, being negligible. Since the total quantity of proteids in the serum varies roughly in an inverse ratio to the amount of water present, we will defer the consideration of their quantitative variations until we discuss the water in the serum.

Our knowledge of the proteids of the blood has undergone a complete revolution within recent years. The researches on immunity have brought to light important functions of the

[88] Pick, Hofmeister's Beitr., vol. i. p. 351.
[89] See Haliburton's Text-Book of Physiological Chemistry.

blood which were hardly suspected previously. The substances which bring about these so-called biological reactions cannot be separated from the proteids by purely chemical means, though we have no direct proof that they are themselves of a proteid nature.

Among the substances under consideration are those which possess the property of accelerating the decomposition of other compounds; [90] *i.e.*, they are of the nature of ferments. If we may assume that the decomposition of different compounds requires the action of different ferments, then the number of ferments present in the blood must be considerable. For the physiologist, such a conception presents certain difficulties. The most varied reactions may be produced by the serum, and it would be necessary to assume a different ferment for each one of these reactions, many of which are apparently absolutely useless. For example, the blood-serum of the carp possesses the property of decomposing trehalose, and yet we have no reason to believe that trehalose is ever present in the blood of this fish.

Substances present in the blood-serum may neutralize certain poisons which may gain access to the blood, a property which is unquestionably of great value to the body.

Cytolytic Properties of the Serum.—The blood-serum is able to destroy many varieties of foreign cells, among them living bacteria. According to our most recent knowledge, two substances participate in this destructive action. One of these possesses the properties of an enzyme,—viz., it is destroyed by a temperature of 56° C. for half an hour, and it acts best at a definite temperature and in a medium of a definite reaction and containing salts in certain proportions. In the blood of healthy individuals, this substance is always present, though in varying amounts. It has been called by

[90] E. Fischer and Niebel, Sitzungsber. der kgl preuss. Akad. der Wissensch., 1896, p. 73.

Buchner the alexin, and by Ehrlich and his school, the complement. Considerable controversy has arisen over the question as to whether there is one alexin in the blood, capable of destroying indifferently a great variety of cells, or whether there are a large number of different alexins present, each possessing a more or less specific destructive action upon certain kinds of cells. The former view has been championed by Bordet and Buchner, the latter by Ehrlich and his school. The latter appears to me to be the more probable. It is supported especially by those experiments in which the serum loses completely its power to destroy one variety of cells while retaining its power to destroy another variety.

The alexins are believed to be produced by the leucocytes, some holding that they are secretions of these cells, others that they become free only when these cells die (Metschnikoff). Metschnikoff has advanced the hypothesis that different varieties of leucocytes produce different forms of alexins.

In discussing the subject of hæmolysis (p. 144), we have already stated that even the alexins of normal serum probably do not act alone. The other class of substances, which assist them, differ from the alexins in that they can usually resist temperatures of 60° C. This second class of bodies is present in normal sera, but only in relatively small quantities. During the process of immunization against foreign cells, however, these bodies become enormously increased. They have been variously designated as the immune bodies (Pfeiffer), substance sensibilisatrice (Bordet), fixateurs (Metschnikoff), and intermediary bodies or amboceptors (Ehrlich). These different names were given to indicate the conception of the namers as to the manner in which the bodies under consideration act.

This second, intermediary body possesses a special affinity for those cells which are susceptible to its action. Owing to this fact, it is possible to remove the intermediary bodies from a serum. To do this, the cells and the serum are allowed to

stand for a certain time in contact at 0° C., at which temperature the intermediary body is bound by the cells, but the alexins are left free in the fluid. If the cells are now removed from the serum by centrifugalization, they carry with them the intermediary bodies, the alexins being left behind. Different varieties of cells possess different affinities, and consequently will remove different intermediary bodies from the same serum. The subject is so intimately related to the theory of immunity that it will be again considered in that connection.

The nature of the relation by which the intermediary bodies are bound to the susceptible cells has been the subject of much controversy, as is illustrated by the various names which have been applied to this body. Gruber and Metschnikoff believe that it favors in some way the action of the alexin on the cell. Bordet believes that it so changes the physical properties of the envelope of the red corpuscle that the alexin can " take hold" on it. Ehrlich regards it as a substance which combines chemically on the one side with the cell, and on the other with the alexin, and in this manner it permits the alexin to come in direct contact with the cell. According to Ehrlich's view, the alexin alone cannot act directly upon the cell, because it cannot combine with it chemically, and it is only through the intervention of the intermediary body that a combination is possible.

Antitoxins: The " Side-Chain" Theory.—The blood-serum is able to neutralize the action of a variety of poisonous compounds. It is not our purpose to discuss the many methods by which the body protects itself against toxic substances. Some are rapidly excreted, some are rendered inert by chemical combinations in the organs, acids are neutralized by an increased production of ammonia, saponin is neutralized by soaps,[91] etc.

If the toxins produced by the diphtheria bacillus be injected into an animal, the blood-serum of that animal will, after a

[91] Ransom, Deut. med Wochens., 1901, No. 13, etc.

time, acquire the property of neutralizing the poisonous action of these toxins. The new substance to which the serum owes this property is called the diphtheria antitoxin. Other substances, among them the tetanus toxin and the various snake venoms, will likewise give rise to the production of antitoxins if they be injected into living animals. Although the antitoxin annuls the poisonous action of the toxin, the latter is not destroyed, for it may be recovered from mixtures of the two by certain manipulations,[92] and it has been demonstrated that the neutralization takes place in accordance with the laws of chemical combination.[93]

All are not yet agreed as to the principles underlying the formation of antitoxin in the body. According to Buchner's conception, the introduced toxin is itself converted into antitoxin by the cells of the body. Behring[94] early expressed the view that the very substances in the living body which are attacked by the toxins are curative if they become free in the blood.

Ehrlich has elaborated the same hypothesis into his now famous " side-chain" theory. If toxic substances of a proteid nature be injected into the circulation, they rapidly disappear from the blood, apparently because they are taken up by the cells. Since, however, they can no longer be recognized in the tissues, a fact which has been demonstrated for certain toxins, it is believed that they have entered into chemical combination with the protoplasm of the cells. Ehrlich assumes that they have combined with peripheral groups of atoms on the large proteid molecules in the cells, which groups he designates as the side-chains. If toxins encounter appropriate side-chains in the body, they are held by such in combination.

[92] Calmette, Inst. Pasteur, 1895, p. 225; Wassermann, Ztft. f. Hyg., vol. xxii. p. 263.

[93] Arrhenius, Berl. klin. Wochenschr., 1904, p. 216.

[94] Deut. med. Wochens., 1898, No. 5.

Ehrlich further assumes that the injury done to the molecule by this fixing of the poisonous toxin on its side-chains acts as a stimulus to the production of new side-chains, similar in character to the ones which were originally injured or destroyed by the toxin. The number of these new side-chains produced is greatly in excess of the number originally destroyed, and the additional ones are thrown off into the circulation, where they remain, ready to combine with any new toxin which may appear there. These free side-chains in the blood, which possess a peculiar affinity for the toxins, are what are known to us as antitoxins. The original injury to the cell may be so severe, however, that the latter is unable to respond to the stimulus, and consequently no antitoxins are produced. The side-chain theory has been given a very wide application, not only to toxins, but to all foreign substances which may combine chemically with the cells of the body. It has been offered as an explanation of the formation of the intermediate immune bodies, of precipitins, agglutinins, etc., and even of the physiological assimilation of proteid food.

It seems to us that the most vulnerable point in Ehrlich's theory is that relating to the production of new chains by the injured molecule. This has been likened to the reaction of tissues to an irritant, which reaction may be so excessive that the new tissue is produced in excess. The two processes are, however, fundamentally different; for, on the one hand, we are dealing with the reaction of living tissue, as a whole, to an injury, while, on the other, it is a reaction involving individual molecules. No reaction, analogous to this one, is known to chemistry.

The organs which clinically seem to suffer most from the infection are usually the ones with which the largest quantities of toxin combine; and it has been demonstrated, for example, that the central nervous system possesses a peculiar

affinity for the tetanus toxin.[95] Yet this is not necessarily the case, and even though the toxins combine with cells in the body, no symptoms may be produced, either because the cells affected are of relatively little functional importance, or because the combination does not seem to greatly harm them. Certain animals, as the hen and the alligator, are practically insusceptible to tetanus, and yet when treated with the toxin, they yield antitoxin in abundance. In such cases it is probable that tissues, other than the nervous system, combine with the toxin without serious damage to themselves and with the production of antitoxin. Immunity to toxins may, however, occur in another way. Thus the tetanus antitoxin will remain in the blood of the turtle for a long time without giving rise either to the symptoms of tetanus or to the production of antibodies. In such a case, we may assume that the turtle possesses no molecules in its cells with which the tetanus toxin can combine.

When cells have been stimulated to the production of antitoxin, they continue to produce it over a long period of time. For this reason the immunity acquired by passing through a disease is more or less durable; for the same reason, the blood of animals strongly immunized may be repeatedly withdrawn, and yet that which is left will always develop new antitoxin,[96] Similarly, the injection of pilocarpin will increase the amount of antitoxin in the blood, probably because it stimulates the internal secretion of the cells.[97]

Though antitoxin occurs in largest quantity in the blood of those who received the toxin, nevertheless it may be present in the blood-serum of a healthy individual, and even, indeed, in the serum of the new-born infant. This remarkable fact, which will be discussed in another place, is explainable in

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[95] Wassermann and Takaki, Berl. klin. Wochens., 1898, No. 1.

[96] Roux and Vaillard, Inst. Pasteur, 1893.

[97] Salomonson and Madsen, Inst. Pasteur, 1897.

accordance with Ehrlich's hypothesis, on the assumption that for some reason the side-chains for which the toxin has an affinity have been cast loose into the circulation.

As a rule, antitoxins act solely or, at least, most energetically upon the toxins that called them into being. Exceptions to this rule, however, do occur, and Calmette has shown that the antitoxin for cobra venom will neutralize the venom of a variety of snakes and scorpions, and that tetanus antitoxin will likewise neutralize snake venom. (Yet even snake venom shows specific differences, for cobra antivenin will not neutralize the venom of the rattlesnake.[98]—Ed.)

The Precipitins.—If proteid substances are injected into an animal, the blood-serum of that animal acquires the property of causing a precipitate when mixed with a clear solution of the proteid injected. The new ·substance in the serum which gives rise to this precipitate is called a precipitin.[99] These precipitins cannot be separated from the globulins of the blood by chemical methods.

The question has arisen as to whether these precipitins are specific tests for the proteids injected; *i.e.*, will the blood-serum of an animal which has been treated with a certain proteid give a precipitate only with solutions of that proteid? This is not apparently the case. The specificity of the reaction seems to depend not upon the structure of the entire molecule injected, but upon the fact that it possesses certain atomic groups, and any proteid which happens to contain these groups might be precipitated by the precipitin. This question is one of considerable practical importance, for the precipitin reaction has been used to distinguish the bloods of different animals. If the blood-serum of an animal, A, be injected into an

[98] Flexner and Naguchi, Jour. of Med. Research, vol. xi., No. 2.

[99] R. Kraus, Wien. klin. Wochens , 1897, p. 736; Wassermann and Schültze, Berl. klin. Wochens., 1901, p. 187; Uhlenhuth, Deut. med. Wochens., 1901, p. 82; Ewing and Straus, Med. News, November, 1903; McHall and Dinkelspiel, Jour. of Hyg., vol. i. p. 367.

٭ animal, B, then the serum of B acquires the property of caus-
ing a precipitate if mixed with the serum of any animal of
the A species, although no precipitate is caused if mixed with
the serum of most other species of animals. If a blood-stain
is suspected to be derived from the A species, it is only neces-
sary to dissolve some of it in water and to test it with the
serum of an animal which is known to have been immunized
against the species A. If a precipitate results, after certain
precautions are taken, it is very probable that the stain really
was from an animal belonging to the species A. In carrying
out such an examination, it is necessary to make use of quan-
titative methods, similar to those used in agglutination tests.
In this way it is possible to eliminate the possibility that the
stain is derived not from the species A, but from some closely
related species A'. Though the latter might cause a precipitate
with the A precipitin, they will do so only in relatively strong
concentrations.

The precipitin reaction is favored by a slightly acid reac-
tion, especially when that is produced by the organic acids,
and the presence of salts of some kind is absolutely necessary.
The precipitins are relatively resistant to unfavorable influ-
ences. Temperatures of 60° C. are borne for a considerable
time, and drying or even putrefaction does not destroy them.

Agglutination.—If foreign cells or bacteria be injected
into an animal, the blood-serum of the latter acquires the
property of causing these cells to collect in clumps, which fall
to the bottom of the vessel leaving a clear fluid above them.
This reaction is called agglutination.[100]

The relation of the process of agglutination to the de-
struction of foreign cells is not yet perfectly clear. Some hold
that the agglutinins are closely related to the intermediary
bodies which assist in the destruction of foreign cells, and

[100] Gruber and Durham, Münch. med. Wochens., 1896, p. 285; Gruber,
Münch. med. Wochens., 1899, No. 41.

which are also produced during the process of immunization; yet many facts indicate that the two are quite distinct. Agglutination seems to be caused by changes in the enveloping membranes of the cells which are agglutinated.[101]

The blood-serum therefore contains a great variety of substances, and is possessed of the most varied functions. Our knowledge of these matters is only in its infancy, and no one dares to surmise what the future may bring forth. According to the Ehrlich hypothesis, the agglutinins, precipitins, antitoxins, intermediary bodies, etc., are derived from the cells of the body. We know little concerning the source of the normal proteids of the blood, such as the albumin, the globulins, and the fibrinogen; yet the differences in the bloods of different animals, as demonstrated by the precipitin reactions, would lead one to believe that these proteids are, in part at least, the products of cellular activity, and, as such, are quite independent of the character of the nourishment taken. It seems probable, indeed, that the proteid food not immediately consumed in the metabolism of the body is taken up by the cells and is transformed by them into the proteids of the plasma.

The question as to the chemical nature of the various antibodies, particularly of the diphtheria and tetanus antitoxins, has been studied by Pick.[102] He has shown that they are precipitated along with the globulins of the serum. The chemical characteristics of diphtheria antitoxin vary according to its source; that from the goat being precipitated with euglobulin and that from the horse with pseudoglobulin. Such differences were not discovered for the tetanus antitoxin, but were found true for certain agglutinins. These facts support the view that the "biological" properties of a substance depend not so much upon its total molecular composition as upon the possession of certain groups of atoms.

[101] See Sick, Arch. f. klin. Med, vol. lxxx. p. 389.
[102] Hofmeister's Beitr., vol. i p. 351.

The Salts of the Serum.—The salts of the serum are, for the most part, made up of sodium chloride, sodium carbonate, and the phosphates of the alkalies. Other salts are present only in minimal quantities, and some, such as calcium phosphate, are present in the plasma, but are removed from the serum by the fibrin during coagulation. The variations of the salts of the blood in health and in disease have never been satisfactorily worked out, which is unfortunate, for without doubt the salts exercise an important influence upon the blood-corpuscles and upon the proteids of the plasma.

The Percentage of Water in the Blood. Hydræmia.—The relative amounts of proteids and water in the serum vary even in health, although the limits of these variations are not accurately known. The variations in disease have only been partially studied; but we know that they frequently remain within the normal limits, even in the most severe diseases. The most evident thickening of the blood—*i.e.*, the greatest relative increase in the proteids—is seen in Asiatic cholera, and depends upon the loss of fluids from the body.

When the unit of blood is deficient in proteid material, we speak of an hydræmia, a watering of the plasma.[108] This condition frequently develops as a result of emaciating diseases. If the heart and kidneys are in order, the hydræmia is probably due to a primary diminution in the proteids of the blood, although we must remember that a destruction of the proteids of the body does not necessarily produce a watery condition of the plasma. Among the emaciating diseases which may produce an hydræmia of this character are inanition, repeated hemorrhages, anæmias, malignant tumors, and severe chronic infections. Although an hydræmia frequently develops in the above diseases, nevertheless it does not necessarily do so. We are not justified, therefore, in concluding

[108] v. Limbeck, Prag. med. Wochens., 1893, No. 12; Hammerschlag, Ztft. f. klin. Med., vol. xxi. p. 475.

that a rapid consumption or a diminished supply of proteid material is alone responsible for the hydræmias of this class. Other factors, at present little understood, undoubtedly play a part. Until we know more of the functions and source of the proteids of the plasma, it will be impossible to harmonize the many contradictory facts relating to this class of hydræmias.

It is possible that an hydræmia should be caused, not by a primary reduction of the proteid constituents of the blood, but by a primary increase in the amount of water. The hydræmias associated with the diseases of the kidneys and with cardiac insufficiencies are probably partly of this nature. According to Hammerschlag, chronic interstitial nephritis rarely causes a watery condition of the blood, and chronic parenchymatous nephritis sometimes fails to do so. Hydræmia is frequently present in the latter, however, and it is most marked when there is polyuria. Under such circumstances, the specific gravity of the blood may fall from the normal of 1.030 to 1.020. Other observers have obtained results which differ somewhat from those of Hammerschlag; yet some of these, based upon total nitrogen determinations, must be rejected as inaccurate, on account of the frequent retention in nephritic blood of other nitrogenous bodies than proteids.

The hydræmia which is undoubtedly present in many cases of nephritis can be caused only in part by the loss of albumin, for the hydræmia and the amount of albumin in the urine bear no definite relation to each other. In many cases of nephritis, water is retained in the body, for less is excreted through the kidneys and often less also through the skin. These two factors—the loss of albumin in the urine and the retention of water in the body—are sufficient to explain the hydræmia present in many cases of nephritis, though hardly in all, for some patients with hydræmia are excreting large amounts of urine. (The cause of the retention of water has

recently been attributed to a primary insufficiency in the excretion of sodium chloride through the kidneys, the retained water serving merely to dilute the retained salt. In support of this hypothesis, we have Widal's observations that, in certain cases of nephritis, the œdema disappears with almost miraculous rapidity if the ingestion of chlorides be restricted.[104]—ED.)

Certain patients, suffering from heart disease in the stage of broken compensation, show a watery condition of the blood; both the specific gravity and the proportion of proteids in the blood being diminished.[105] A weakness of the right ventricle is especially apt to give rise to such a thinning of the blood. When the circulation improves and the venous pressure falls, then the blood tends to return to its normal composition. This hydræmia occurs in a comparatively small proportion of all cases of broken compensation; but, where it does occur, it is quite usual for it to disappear with any improvement in the circulation. In these cases, the loss of proteids from the blood is not usually very great, but there is frequently a retention of water which would tend to dilute the blood.

It seems very probable to us that the hydræmias which accompany cardiac and renal diseases are for the most part caused by such a retention of water in the body; that there is, in fact, an increased quantity of watery blood in the body, a so-called hydræmic plethora. Such an hypothesis would well explain the fact that with the development of a cardiac insufficiency not only the proteids, but the number of corpuscles to the unit-volume of blood, is diminished, and that, with an improvement in the circulation, the blood again becomes normal. There is no reason why the blood should not become œdematous just as do the tissues. Possibly, the water is held

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[104] See, for example, the case described by Widal and Javal, International Clinics, fourteenth series, vol. i. p. i.

[105] Grawitz, Arch. f. klin. Med., vol. liv. p. 588.

back in the body by substances which attract it (see p. 175). Grawitz believes that the increased amount of water in the blood is derived from the lypmh which diffuses into the capillaries, owing to the low pressure existing there. Yet we know that in the conditions under consideration fluids pass from the capillaries into the lymph-spaces, so that these become distended. The relations must therefore be quite complicated and the final results dependent upon which process takes place the more rapidly.

Polycythæmia.—In not a few cases of chronic stasis, the capillary blood is more concentrated than normal. At least it contains many more red blood-corpuscles and correspondingly more hæmoglobin to the unit-volume. The composition of the serum in these cases has not yet been finally settled, but good observers have found it to be diluted.[106] This increase in the number of the erythrocytes is found especially in cases of long-continued venous stasis, such as occur in congenital heart lesions, in chronic pulmonary disease, and in insufficiency of the right ventricle. Investigations thus far have all been made upon the blood of the cutaneous capillaries or veins, so that we are unable to discuss the relative concentration of the blood in the different vessels of the body;[107] yet the possibility exists that in these cases of stasis, the blood of the peripheral vessels contains more corpuscles than does the blood of the remainder of the body, and the question can only be decided by studies on fresh cadavers or upon animals with heart lesions.

The number of erythocytes in these cases is often very great,—from six million to eight million per cubic millimetre; and, at the same time the serum is usually more dilute than normal. This latter fact would seem to indicate that the increased number of corpuscles is not due to a loss of water

[106] Hammerschlag, Grawitz, loc. cit.
[107] Grawitz, Arch. f. klin. Med., vol. liv. p. 588.

from the blood. Marie and Hayem explain the increase in the number of red blood-corpuscles as a compensatory process which tends to neutralize the insufficient oxidation of the blood caused by the stasis;[108] yet since their theory presupposes an increase in the number of corpuscles throughout the whole body, it rests upon an insecure foundation.

It is possible that the polycythæmia is primary in certain cases; *i.e.*, that it occurs without demonstrable cause. At least, there have been some remarkable cases reported in which chronic cyanosis, enlargement of the spleen, albuminuria, and increase in the number of the red corpuscles have been observed without any considerable venous stasis.[109]

Extremely interesting are the changes which take place in the blood when an animal passes from a region of high to one of low atmospheric pressure. Within a short period of time the number of red corpuscles to the cubic millimetre of blood becomes increased, and the hæmoglobin also increases, but more slowly. These increases affect the blood of all parts of the circulatory apparatus, though they are less marked, perhaps, in the arteries than in the veins and capillaries of the skin. The higher the elevation, the greater is the number of red corpuscles. The highest figures which have been reported are from the Cordilleras, at an elevation of over twelve thousand feet.[110] All the animals at these heights have an extraordinary number of red corpuscles; *e.g.*, the llama has sixteen million to the cubic millimetre. The amount of gas in the blood is, however, about the same as in the blood of animals at lower levels. When a man or animal descends from these heights to the sea level, the number of red cells diminishes correspondingly. There is almost universal agreement

[108] P. Marie, Mercr. méd., 1895, No. 3; Hayem, ibid., No. 4.

[109] Osler, Am. Jour. of the Med. Sci., August, 1903.

[110] Viault, Compt. rend. de l'acad. des sci., vol. cxi. p. 917; vol. cxii. p. 295.

among authors in regard to the increase in the number of erythrocytes per unit-volume at high elevations, and the few negative observations [111] are due probably to too short a stay at the high altitude. At any rate, there is usually an increase in the number of the red cells per unit-volume at high altitudes.

This increase is unquestionably caused by the low atmospheric pressure, for it can be produced experimentally by subjecting animals to low pressures under the air-pump.[112] Some consider that the total number of red cells in the body is actually increased in such cases, and that this serves to compensate for the lessened pressure of the oxygen in the lungs. If, indeed, new cells are formed, we have little microscopical evidence of it, for nucleated red corpuscles have been seen by very few,[113] and most authors expressly state that they were absent. Furthermore, it is difficult, on such an hypothesis, to account for the rapid disappearance of red cells when the animal returns to a lower altitude, for positive signs of a destruction of red corpuscles, such as jaundice and a deposition of iron in the liver, have not been observed under these conditions. Yet we know that the absence of these signs is by no means absolute proof that no destruction of the red cells has taken place, for they have been missed in cases in which an extensive destruction certainly had occurred.[114]

Another explanation that has been offered for the increase in the number of the erythrocytes at high altitudes, is that it is due to a loss of water from the blood; yet this meets with almost equal difficulties. Beyond question, the dryness of the air, the exposure to the sun's rays, and the deeper respirations increase the loss of water from the body, yet a healthy

[111] Schumburg and Zuntz, Pflüger's Arch., vol. lxiii. p. 492; Egli-Sinclair, Wien. med. Blät., 1895, Nos. 8 and 9.

[112] Grawitz, Berl. klin. Wochenschr., 1895, Nos. 33 and 34; Schauman and Rosenquist, Ztft. f. klin. Med., vol. xxxv. pp. 126, 315.

[113] Gaule, Pflüger's Arch., vol. lxxxix. p. 119.

[114] Lesser, Verh. der Säch. Gesell. d. Wissenschf., 1874, p. 153.

man would ordinarily replace this water by taking more fluids by the mouth. The supposed loss of water should also lead to a more concentrated serum, as well as to an increased number of red blood-corpuscles, and it is very doubtful if this concentration of the serum actually occurs. The sera of two rabbits in Basel contained 7.62 and 7.96 per cent. of solids respectively, whereas in Arosa, at a high elevation, the percentages were 7.79 and 8.02, an inconsiderable change compared with the changes in the erythrocytes.[115] Grawitz found some increased concentration in the sera of animals which had been kept under low pressures in Berlin, but here again the increased concentration was in no way proportional to the increase in the number of the red blood-corpuscles. Furthermore, a concentration of the blood by evaporation is only possible when the tissues likewise lose large quantities of water,[116] and such a loss of weight certainly does not occur either in men or in animals subjected to low atmospheric pressures. Finally, an increase in the number of erythrocytes also takes place when the animals are prevented from losing excessive amounts of water by being kept in rarified air saturated with water vapor.

According to a third theory, the increase in the number of red blood-corpuscles at high elevations is due to the passage of plasma out of the blood-vessels into the lymphatic system. At present this seems to be the most plausible explanation for the known facts; yet it is also open to objections, especially to the fact that the red blood-corpuscles and the hæmoglobin do not increase at precisely the same rate.

The crucial test for deciding whether or not the hæmoglobin actually increases at high altitudes would be the determination of the total quantity of hæmoglobin in the body. If this be increased in animals exposed to low atmospheric

[115] Egger, Kongr. f. in. Med., 1893, p. 262.
[116] Czerny, Arch. f. exp. Path., vol. xxxiv. p. 268.

pressure, then we may assume that there is, indeed, a total increase in the red blood-cells and in their pigment under these influences. Unfortunately, the experiments which have been undertaken to decide this point have given contradictory results. Some observers found no increase in the total amount of hæmoglobin in the body,[117] others have found a slight increase,[118] while still others have found a marked increase.[119] The inaccuracies in the methods for determining the total hæmoglobin in the body probably account for these discrepancies in results.

An increase in the number of the red blood-corpuscles to the unit-volume is also seen in phosphorus and carbon monoxide poisoning, but we are ignorant as to its exact cause.

Plethora.—There is no reason *a priori* why an increase in the total quantity of blood in the body should not take place, for it is known that the parenchyma of other organs may increase in bulk. It is, however, impossible to obtain direct proof of such an increase so far as human blood is concerned, for as yet we have no accurate method of determining the total quantity of the blood in man.

The doctrine of an increased quantity of blood, a true plethora, played a great rôle in the older hæmatology, and various symptoms were believed to be caused by the "full-blooded" condition of the patient. While we must acknowledge that many of these cases will not stand the rigid criticism of modern times and that the anæmia of many of these individuals was the probable cause of their symptoms, yet there are certain facts which favor a belief in the occurrence of a true plethora. Thus many patients feel better after having been bled, and although this fact is in no sense a proof that a condition of plethora existed previous to the bleeding, yet it

[117] Bunge and Weiss, Ztft. f. phys. Chem., vol. xxii. p. 526.
[118] Abderhalden, Diss. Basel, 1902.
[119] Jaquet, Arch. f. exp. Path., vol. xlv. p. 1.

cannot be entirely disregarded. More important is the testimony of such pathologists as v. Recklinghausen and Bollinger who give it as their impression that at autopsy many bodies seem abnormally rich in blood. That the amount of blood in animals may vary greatly not only in different species, but in different individuals of the same species, has been definitely proved by the work of Bergmann and Bollinger.[120] They have demonstrated that the character of the food may exert a marked influence upon the total quantity of blood in the bodies of animals.

We are justified in suspecting a condition of plethora whenever an individual, who habitually consumes excessive amounts of food and drink, and who has large muscles and much fat, shows a continual hyperæmia of the surface of his body, and has an enlarged heart, a full pulse, and wide arteries. Although we may be unable to prove that a plethora exists in such individuals, nevertheless the experience of pathologists and the experimental evidence above referred to, both justify such a probable diagnosis.

Certain observations seem opposed to the doctrine of plethora, more especially the fact that if animals are infused with sera or salt solution, the excess of fluid is rapidly removed from the circulation, and no increase in the total quantity of blood is produced. Yet the conditions of such an "acute" experiment are quite different from the chronic changes which are believed to lead to plethora in man, and furthermore, it is quite possible that under pathological conditions there may be an inability to thus remove large quantities of fluid from the circulation.

We hold, therefore, that although the doctrine of a true plethora has not been absolutely proved, its existence is very probable. The long-continued ingestion of excessive amounts of food seems to be the most potent causative factor. Yet it is

[120] Bollinger, Münch. med. Wochens., 1886, Nos. 5 and 6.

apparently only one factor, and others of which we are now ignorant may play a part in its causation.

The doctrine of a diminution in the total quantity of blood is as little capable of direct proof as is the doctrine of plethora. Yet the impression prevails among clinicians, as well as among pathologists, that it does exist, and that in the severe anæmias, especially, there is a diminution not only in the number of cells to the unit of volume, but in the quantity of blood as a whole.

CHAPTER IV.

INFECTION AND IMMUNITY.

In this chapter we propose to consider the various means by which the animal body resists the invasion of pathogenic micro-organisms.[1]

The Portals of Entry.—The surfaces of the body are covered with innumerable bacteria. They live upon the skin and upon the mucous membranes of the mouth, the nose, the trachea, the vagina, and the gastro-intestinal canal. The majority of these bacteria are quite harmless; yet virulent ones, such as the diphtheria bacilli, pneumococci, and streptococci, are not infrequently present, without necessarily doing any harm.

These surfaces must, therefore, act as barriers to the entrance of bacteria; mainly because the intact epithelium opposes great resistance to the passage of any solid particles through it. For example, the mercury in blue ointment is apparently converted into a fatty-acid salt before it is absorbed,[2] and fats are absorbed by the intestines only after they have been brought into solution. On the other hand, we know that leucocytes may wander in and out between the epithelial cells, and it seems probable that they may carry bacteria back within them. If, after being thus carried into the body, the bacteria survive the ingestion by the leucocytes, they might cause disease; though how frequently an infection takes place in this manner is entirely unknown.

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[1] Aschoff, Ehrlich's Seitenkettentheorie, etc.; v. Behring, Deut. med. Wochens, 1898, No. 5; Ehrlich, Gesm. Abhandl. ü. Immun., Berlin, 1904; Metschnikoff, Immunity.

[2] Schmiedeberg, Grundr. d. Arzneimittellehre, 4th. ed.

In many acute infections there is present an obvious injury of the epithelium, which permits the entrance of bacteria into the body, as is well illustrated in the case of the skin. Tetanus, malaria, and the various wound infections nearly always gain admittance to the body through an injury of the cutaneous epithelium.

Our knowledge of the method by which infections enter through the mucous membranes is less accurate. Tonsillar diseases appear to play an important rôle in predisposing to infections with the pyogenic cocci. The wandering of the leucocytes through the epithelium of the tonsils and the frequent local lesions render them especially permeable to bacteria, and liable to be the gate-way which admits a general invasion of microorganisms.

The air-passages of healthy individuals, below the upper part of the trachea, are, as a rule, sterile.[3] Yet should the bacteria penetrate to the lungs themselves, the delicate epithelium of the alveoli would hardly prevent them from passing through. At any rate, we know that solid particles, if inhaled in great numbers, are often deposited in the pulmonary tissues, as occurs in the dust diseases. Many observers believe that bacteria may also enter the lungs in a similar manner whenever many are present in the inspired air. Such invaders may cause diseases of the lungs themselves, or they may be carried to the neighboring lymphatic glands, there to grow or to be destroyed. The lungs appear to possess considerable ability to destroy bacteria which may reach them,[4] and even though they become inflamed, this inflammation may protect the remainder of the body from a general invasion. Indeed, it seems to be rare for a general infection to gain admittance to

[3] F. Müller, Münch. med. Wochens., 1897, No. 49; Klipstein, Ztft. f. klin. Med., vol. xxxiv. p. 191; opposed to these is Dürck, Arch. f. klin. Med., vol. lviii. p. 368.

[4] Snel, Ztft. f. Hyg., vol. xl. p. 103.

the body by way of the lungs without producing a primary disease of these organs or of their lymphatic apparatus.

The main protection of the lungs against the entrance of bacteria is the winding path through which the air must travel in the nose, the pharynx, and the larynx. Solid particles in the air are caught by the mucus which covers this passage, and, although this mucus possesses but little bactericidal power, yet it is at least a poor culture medium, and the bacteria, when caught, do not multiply. The current in the mucus, caused by the ciliated epithelium, is so directed that it tends to carry all particles out through the trachea.

The factors which favor an infection of the air-passages have been accurately determined in animals,[5] but our knowledge, so far as man is concerned, is more limited. A large number of micro-organisms in the inspired air undoubtedly favors infection, especially if, at the same time, the individual breathes deeply. The virulence of the bacteria inhaled is likewise of importance, and, finally, an inflammation of the upper air-passages greatly favors the migration of bacteria down into the lungs. Cooling or wetting of the surface of the body is generally believed to favor the development of infectious processes in the bronchi and lungs, and this is possibly so because the epithelium is injured by such agents. If the air does not pass through the winding upper respiratory tract, infection of the lungs is much more liable to take place. For this reason, a tracheal canula is always a menace, and many animals with weak respiratory muscles are practically certain to die if they breathe through such a canula. For this reason, also, inflammations of the air-passages are relatively frequent in mouth-breathers.

The gastro-intestinal tract is continually receiving micro-organisms which have been swallowed in the food. Some of

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[5] Klipstein, Ztft. f. klin. Med., vol. xxxiv. p. 191; Göbell, Diss. Marburg, 1897.

these are quickly destroyed by the action of the acid in the gastric juice; yet, since the stomach begins to empty itself shortly after the food enters, and since the first acid secreted is bound by the proteids of the food, and since, finally, the gastric juice does not reach the interior of many large food particles, there always exists the possibility that virulent organisms will pass through the stomach into the intestines.

Once in the intestines, it becomes a question as to whether or not the bacteria will penetrate the intestinal walls. We may say, in general, that solid particles do not readily pass through these walls, and that, with but few exceptions, all experiments have tended to show the effectiveness of the epithelial barrier. Yet we possess indirect evidence that bacteria may pass through the walls of the intestines. Typhoid fever is apparently contracted in this manner, and tuberculosis has been produced experimentally in animals by feeding them bacilli. Do these organisms, however, pass through an intact mucous membrane, or is a primary lesion of the epithelium necessary? Baumgarten has shown experimentally that tubercle bacilli rapidly disappear from the intestinal contents, and that a few may afterwards be found in the lymphatic follicles and glands of the intestines.[6] They seem to be carried in during the absorption of food. The manner in which each different organism penetrates the intestinal wall must, however, be studied separately; for when an organism grows in the intestinal contents, as do the cholera and probably also the typhoid bacilli, then it may readily produce a slight injury of the epithelium through which it penetrates to the blood.

Yet even if we admit that bacteria can penetrate the uninjured intestinal wall, they certainly do not do this easily, and many circumstances influence the process. In the first place, the number of bacteria present is of great importance.

[6] Ztft. f. klin Med., vol. x. p. 49.

Then, too, a rapid transit through the intestines may serve as a protection against invasion. Possibly this is the reason that many diseases of the intestines, such as typhoid fever, affect principally the ilium, where the passage of the contents is slower than it is in the jejunum, and where the organisms have a better chance to cling to the walls and to grow into them.[7] The normal flora of the intestines may be able to protect us from disease by killing off strange bacteria, and many pathogenic micro-organisms, if introduced into the intestines, rapidly disappear without giving rise to any symptoms.

The relations in the vagina are somewhat similar to those in the intestines. There, also, we have a normal flora, which may injure strange invaders, and the acid reaction of the secretions of the vagina is unfavorable to the development of most pathogenic bacteria.[8]

From all that has been said, we see what numerous defences against the invasion of micro-organisms are present on the surfaces of the body. The difficulty of passing the intact epithelium, the acidity and bactericidal properties of many of the secretions, the conflict with the normal flora and with the leucocytes on the surfaces,—all these serve to protect the body from the entrance of bacteria. In recent years there has been a tendency to lay too great stress upon the protective mechanisms which are called into play after the organisms have entered the body. v. Behring has called attention to the fact that an animal may be highly susceptible to inoculation with a micro-organism, and yet be quite insusceptible to the corresponding natural disease, apparently because it is able to prevent the entrance of the organism to its body (mouse anthrax[9]). The defences of the body, therefore, begin at its surfaces, and these defences are of no little importance.

[7] Bienstock, Die med. Woche, 1901, Nos. 33, 34.
[8] Menge and Krönig, Bakt. d. weib. Genitalkanals, Leipzig, 1897.
[9] Diphtherie, in the Bibliothek Coler, Berlin, 1901, p. 95.

Natural Inherited Immunity.—The ability of different persons to resist infection varies. Of the many exposed to a disease, only certain individuals contract it, although we may frequently be certain that many others have received the pathogenic bacteria into their bodies. Certain bacteria may be very pathogenic for one species of animals, and yet be almost without effect upon other closely related species. Even the resistance of the same individual varies under different circumstances.

Bacteria which have been introduced into the body may be rapidly destroyed without producing any symptoms of disease; in which case the animal is said to be immune to the disease in question. This immunity may be an inherited one, or it may have been acquired by having had the disease in question, or, finally, it may have been produced artificially by means which will be discussed shortly.

In the immune animal, organisms are rapidly destroyed without producing any harmful effects. How is this accomplished? We know that bacteria are very susceptible to changes in the medium in which they live, and some have held that such changes cause the death of bacteria which have been introduced into the body. For example, unfavorable osmotic relations may kill bacteria, and changes in temperature may also be unfavorable to bacterial growth; but it is doubtful if such changes exert any considerable influence in protecting warm-blooded animals, at least, from bacterial invasions.

The plasma and serum of the blood are frequently able to destroy bacteria or to neutralize bacterial toxins.[10] Of this there can be no doubt. When bacteria are placed in a serum possessing bactericidal properties, they are broken up into small granules and ultimately dissolve, which solution may or may

[10] Nuttall, Ztft. f. Hyg , vol. iv. p. 253; Nissen, Ztft. f. Hyg., vol. vi. p. 487; Behring and Nissen, Ztft. f Hyg., vol. viii. p. 412, and vol. ix. p. 95.

not be preceded by an agglutination of the bacteria. This bactericidal property is lost if the serum be heated to 56° C. for half an hour. It seems very unlikely that such a temperature should change the nutritive or osmotic characters of the serum to any great extent, and for this reason it has been assumed that the bactericidal properties of the fresh serum are due to the possession of a ferment-like body, which is unable to resist a temperature of 56° C. These bactericidal substances are present, not only in the blood, but in the lymph and in extracts of various tissues.

Yet the natural immunity of an animal and the bactericidal properties of its serum do not necessarily vary together. They do, indeed, do this in many instances, as, for example, in the case of the white rat, which possesses both a natural immunity against anthrax and a blood-serum which is capable of destroying anthrax bacilli. On the other hand, there are many exceptions to this rule. For example, the blood-serum of rabbits will destroy anthrax bacilli, whereas the animals themselves are susceptible to the disease.

Natural Acquired Immunity.—An immunity against future attacks is frequently acquired by having passed through a disease; though not every disease leaves the patient thus immune against future attacks. Such an acquired immunity is most marked after the acute exanthemata. After typhoid fever it may last many years, or may, indeed, be permanent. Diphtheria and cholera reduce the susceptibility to future infections only for a very limited period of time. Pneumonia does not even do this, and erysipelas seems to leave behind, in many persons, an increased susceptibility to future infections. No relation exists between the severity of the infection and the degree of immunity acquired by having passed through it; and it is a well-known fact that the mildest form of a disease may endow the individual with a substantial protection from future attacks.

The cause of the immunity which results from the acute exanthemata has not been studied, mainly because we are ignorant as to the etiology of these diseases. The immunities resulting from typhoid fever and cholera have been carefully studied, and we know that they are associated with an increase in the bactericidal power of the blood. This increase in bactericidal power holds, not for all bacteria, but only for those which were the cause of the disease, or, in some instances, for . closely related species also. Such a *bactericidal immunity* is identical with that acquired against other foreign cells which may have been injected into an animal, and the subject has already been discussed in speaking of the hæmolytic power acquired by the injection of red blood-corpuscles (see p. 143).

An acquired immunity does not, however, necessarily depend upon an increase in the bactericidal properties of the blood. In certain diseases it is due to the production of bodies which will neutralize the bacterial toxins; *i.e.*, it is an *antitoxic immunity*. The majority of bacteria seem to harm the animal by the poisons which they produce, though the existence of such poisons has not been demonstrated for all, notably not for the anthrax bacillus. The classical examples of organisms which do produce such toxins is furnished by the diphtheria and tetanus bacilli. The danger of infections with these bacilli lies not so much in the extent of their growth as in the amount and virulence of the toxins absorbed, even when the infection itself is purely local.

In some instances the toxins are to be regarded as the secretions of living bacteria, while in other cases they seem to be set free only when the bacteria die and their bodies pass into solution. The exact nature of this second class of toxins is very little understood.

We know but little concerning the chemical nature of toxins. They are precipitated along with certain forms of proteids, but it is very questionable if they are proteids them-

selves. Their extraordinary toxicity and the fact that they are extremely susceptible to heat incline one to believe that they are of the nature of ferments.

The method of dissemination of the tetanus toxin is quite different from that of any known alkaloidal poison. While the latter are carried to the susceptible cells by the blood-current, the tetanus toxin travels through the nerves from the point of infection to the central ganglion cells, where it exerts its poisonous actions.[11] These ganglion cells cannot be reached by way of the blood-current, though they are affected by injections of the toxin directly into the nerves or into the spinal cord. When the injections are made into the cord, the incubation period, intervening before the development of symptoms, which is otherwise so prolonged in tetanus, is much shortened or entirely absent. The incubation period for tetanus, therefore, appears to be the time consumed by the toxin in travelling from the point at which it enters the body to the cells upon which it exerts its poisonous action. This mode of dissemination explains the fact that in experimental tetanus the spasm first develops in the extremity infected; for the toxin, travelling up the nerve, first acts upon the corresponding part of the cord. In man, however, the muscles of the jaw are usually first affected. The diphtheria toxins, in so far as they affect the nervous system, may likewise travel along the nerves, for it is a well-known clinical fact that the nerves most frequently paralyzed are those which are situated in the neighborhood of the local lesion.

Bacterial toxins, introduced into the body, lead to the formation of substances which possess the property of neutralizing the toxins introduced. These antitoxins have already been considered in another place (p. 167), and are of the utmost importance in the process of recovery from a disease.

Besides the protection afforded to the body by the produc-

[11] Meyer and Ransom, Arch. f. exp. Path., vol. xlix. p. 369.

tion of antitoxins and bactericidal substances, the natural resistance may be increased by still other substances, which are not specific in their action.   Years ago, Wooldridge showed that animals could be protected from anthrax by injections of his "tissue fibrinogen;" and since then we have become acquainted with a great number of means which are more or less protective against a great variety of infections.[12]   The immunity conferred by these means, however, is *non-specific* for a single bacterium, and is less certain, weaker, and less durable than is the immunity conferred by the specific antibodies; though, as we shall see, the passive, acquired immunity is also of a fleeting character.

The acquired, specific immunity may, therefore, be produced by changes in the fluids of the body, in which case it is usually either a bactericidal or an antitoxic immunity.

Active Artificial Immunity.—Immunity to an infection may also be induced by certain artificial means.   There are two general methods of producing such an artificial immunity. In the first, the organism which causes the disease, or some material derived from it, is injected into the individual to be immunized.   The latter then passes through a sickness with fever, etc., following which he becomes more or less immune to future infections with this same organism.   An immunity acquired in this manner is termed an isopathic or active immunity, because it is acquired by having had the disease.   In practising this form of immunization, the material used is either injected in very small amounts or its virulence is weakened, so that the animal shall acquire the disease in a mild form.   The immunity following such procedures develops gradually, but it is very durable, and even though antibodies are withdrawn from the body by bleeding, new ones are formed.   As examples of active artificial immunization, we may name the antitoxic immunity of horses treated by injec-

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[12] Buchner, in Penzoldt-Stintzing, third ed., p. 119.

tions of the diphtheria toxins, the immunity against anthrax acquired by animals after injections with attenuated anthrax bacilli, the Pasteur treatment of rabies, and, finally, if we regard vaccinia as attenuated variola, the immunity to smallpox which follows vaccination.

Passive Artificial Immunity.—The second form of artificial immunity is produced by the injection into the animal body of antibodies which have been produced in another animal. For this purpose it is usual to use the blood-serum of animals which have acquired an active immunity to the disease in question. This passive immunity appears immediately after the injection, but it soon disappears, usually in the course of a few weeks, probably because antibodies produced in another animal are in the nature of foreign substances, and so are rapidly eliminated. The cells of the immunized animal seem to take no part in the process of passive immunization.[18] Passive artificial immunity may be theoretically produced either by the injection of substances which will neutralize the bacterial toxins or by substances which will kill the bacteria. Practically, however, the latter (bactericidal sera) have not proved very successful, and the most notable examples of this method of immunization are the immunities produced by the injection of diphtheria and tetanus antitoxins.

Phagocytosis and Immunity.—Up to this point we have discussed mainly the relation of the fluids of the body to the condition of immunity. There is, however, a school which places greater emphasis upon the part played by the living cells in the defence against disease. Wandering cells, partly leucocytes and partly derivatives of the fixed cells of the tissues, may pick up solid particles of all kinds and carry them away. Such cells are usually found in the neighborhood of solid particles, and they not only remove the latter mechanically, but may dissolve completely the substances ingested. This

[18] Fraenkel and Solbernheim, Hyg., Rundschau, 1894, pp. 97, 145.

solution of foreign bodies appears to be accomplished through enzymes within the wandering cells. Sometimes the ingested body is not entirely dissolved, but is broken up into many smaller particles, which are removed with comparative ease on account of their small size.

These wandering cells appear during the course of many infectious diseases. As has been stated in another place, they are attracted to the point of infection by substances derived from the bacteria in question. The process of picking up and removing foreign bodies in this manner is called phagocytosis, and the theory that immunity depends largely upon the phago-cytic properties of the cells has been developed especially through the work of Metschnikoff and his school, and has been defended by them with wonderful skill against numerous attacks.[14]

That wandering cells do pick up bacteria is established beyond question, and that they will pick up living bacteria is likewise certain, for Metschnikoff was able to cultivate anthrax bacilli which had previously been taken up by the leucocytes. In many infectious diseases, the greater number of bacteria present are found within wandering cells at the point of in-fection. Yet there are certain infections in which no such phagocytosis is to be seen, and in such the defences of the body must reside in its fluids; though Metschnikoff's con-tention that the protective properties of the fluids themselves are derived from wandering cells is not easily disproved.

Conclusions.—No one theory of immunity, therefore, ap-plies to all cases, and it is very questionable if the body limits itself to one method of defence against the attacks of invading bacteria. Perhaps different methods are used in different cases, according to the manner in which the invading micro-organism attacks the individual.

The body fluids of a person who is immune, either naturally

[14] Metschnikoff, Immunität bei Infectionskrankh., Jena, 1902.

or from having had the disease, may in certain instances possess the property of killing the invading micro-organisms or of neutralizing their toxins. In other instances, the wandering cells may pick up the bacteria and destroy them. Both processes may afford protection against the invasion of bacteria, yet instances are known in which neither seems to explain the immunity present,—e.g., the immunity of turtles against tetanus toxin (p. 170).

In those infectious diseases in which the micro-organism does harm by means of the toxins which they produce (and this may be the case in all infectious diseases) death results if the amount or the virulence of the toxins cannot be neutralized by the infected animal. Cure follows the formation or the artificial introduction of a sufficiently large amount of antitoxin. We know that diphtheria bacilli are readily killed by the body if their offensive weapons, their toxins, can be rendered inert. But it also appears to be possible that the cure could result from a dying out of the bacteria even though their toxins have not been neutralized by antitoxins. Finally, the toxins, even though present, may cease to have power to affect the cells, for the reason, apparently, that the cells possess no molecules with which these toxins can combine, as has been shown especially for tetanus.[15] From a consideration of all these facts, it is evident that the protection which an animal enjoys from an infection may be due to any one or several of various factors, and that at present we are merely standing on the threshold of an accurate knowledge of the various means by which the body is protected against disease.

[15] Vincenti, Deut. med. Wochens., 1898.

CHAPTER V.

THE RESPIRATION.

THE cells of our bodies continually receive oxygen from the blood and continually give up the carbon dioxide formed in their metabolism to the blood- and lymph-streams. In the lungs the blood takes up a new supply of oxygen from the inspired air and unburdens itself of the carbon dioxide that it has received from the tissues. These processes, as a whole, are called respiration. The interchange of gases between the tissues and the blood is called internal respiration, whereas that between the blood and the air is called external respiration. Both are intimately dependent upon each other, and the interchange of gases in the tissues, for example, is readily influenced by any changes in the lungs.

The External Respiration.—The first condition necessary for external respiration is the unhindered entrance of air into the lungs. In the pharynx the alimentary and respiratory tracts cross each other, and a special mechanism is therefore necessary to prevent the food from entering the air-passages, where it might produce a serious inflammation. This mechanism will be discussed in another place (p. 235).

Means for removing Harmful Material from the Air-Passages. (a) *Movements of the Cilia.*—If foreign bodies do pass through the glottis into the trachea or its branches, they meet forces that tend to carry them out again. In the first place, there are the cilia on the epithelial surfaces, which, by their slight but continual motion, tend to carry all foreign particles from the bronchioles into the larynx. We are quite ignorant concerning pathological disturbances of the movements of these cilia; which is unfortunate, for it seems probable that a more definite knowledge would aid us in under-

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standing the causation of many diseases of the lungs and bronchi. The movements of the cilia seem to be the most important factor in the removal of foreign particles from the smaller bronchi and the alveoli. Inflammatory material must also be removed from these regions, for otherwise serious harm to the lungs may result.

(b) *The Mucus*.—The second mechanism that aids in protecting the lungs is the secretion of mucus upon the surfaces of the air-passages.[1] Small bodies, such as particles of coal-dust and bacteria, are caught in this mucus, thereby being prevented from penetrating into the air-cells; and after being caught they are carried away by the action of the ciliated epithelium. Only when the secretion of mucus or the movements of the cilia are faulty, or when bacteria are inspired in great numbers, can the latter penetrate into the bronchioles and alveoli.

(c) *Sneezing*.—The secretion of mucus and the movements of the ciliated epithelium are of the utmost importance in cleansing the lungs of foreign material. Certain other mechanisms, however, assist them. For example, many substances are recognized from their odor as being harmful, and these are avoided by the patient. Sneezing tends to remove foreign bodies from the nose. After a deep inspiration, the air is forced out with great velocity, mainly through the nose. The combination of movements which constitute sneezing is initiated by reflexes proceeding from the nasal mucous membrane. Such reflexes are caused either by some excessive stimulation of the normal mucous membrane or by a slight stimulation acting upon a hypersensitive mucous surface.

(d) *Coughing*.—Coughing is correspondingly of great importance in ridding the trachea and larynx of foreign material. It, also, is induced by a reflex mechanism; in the great majority of cases through the pneumogastric nerve.

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[1] Müller, Münch. med. Wochens., 1897, No. 49.

This nerve may be stimulated from the larynx, from the posterior part of the trachea, at the bifurcation of the trachea, from the diseased pleura, from a pathologically enlarged spleen or liver,[2] and, according to the views of many, from the stomach and uterus.[3]

The act of coughing is initiated by a deep inspiration. This is followed by a powerful contraction of the expiratory muscles. At first, the air that should be forced out meets the obstruction of a closed larynx; but later, the vocal cords separate, and through the opening the air is propelled with great violence. The soft palate closes the passage into the nose, and the current of air carries whatever is in the larynx or trachea up into the mouth. Possibly the contents of the larger and even those of the smaller bronchi may be removed by coughing, though this is much less likely to happen. In my opinion, the movements of the ciliated epithelium play the main part in transporting material from the alveoli up to the bifurcation of the trachea. When it has reached this point, the act of coughing readily carries it into the mouth.

The nervous centre for coughing lies in the medulla near the respiratory centre. It is ordinarily excited by reflexes from the regions innervated by the tenth nerve, which regions have just been named. That it may also be directly put into action through cerebral influences is rendered probable by many facts, especially by this, that we are able to cough voluntarily. A reflex cough from the regions that have been named occurs when they have been stimulated beyond a certain point. The amount of stimulation necessary to provoke coughing may, however, vary. We may say, in general, that the irritability of the nerves is increased by acute inflammations of the mucous

[2] Naunyn, Arch. f. klin. Med., vol. xxiii. p. 423.
[3] Edlefsen, Arch. f. klin. Med., vol. xx. p. 200; for a discussion of this subject see A. Fraenkel, Diagnostik and Symptomatologie der Lungenkrankheiten, p. 90.

membranes, so that coughing is then produced by abnormally slight stimulation; while, on the other hand, certain drugs, as well as certain diseases of the brain, diminish the irritability of the nervous mechanism, and so diminish the tendency to cough. Chronic inflammations of the mucous membranes also have this effect in some instances.

In the first class of cases, coughing may be induced by very slight chemical or physical changes in the inspired air; in the second class, no coughing results from stimuli that would otherwise be effective. An absence or weakness of coughing may likewise result from disease of the motor nerves or of the muscles concerned, as has been observed in serious lesions of the nervous system, as well as in patients with general muscular weakness.

A diminution in the ability to cough in response to the normal stimuli is a source of danger, for secretions and foreign bodies are not properly removed from the lungs. This danger is much enhanced when the movements of the ciliated epithelium are also interfered with. Every physician knows and fears the results of such conditions, which are most frequently met in the aged, in those greatly weakened by disease, and during deep narcosis.

Material retained in the lungs decomposes readily. We do not know certainly whether the micro-organisms that cause the decomposition are already present in the lungs, or whether they are introduced from without owing to the lack of protective influences. Personally, I consider the latter the more probable, for many observers have found the normal lungs sterile,[4] though others have found pathogenic organisms in the lungs of healthy animals.[5] At any rate, the act of coughing is normally of great importance in protecting the lungs against

[4] See Barthel, Ztrbl. f. Bakteriol., vol. xxiv. Pt. I. pp. 401, 576.

[5] Dürck, Arch. f. klin. Med., vol. lviii. p. 368; Ztrbl. f. Bak., vol. xlii. Pt. I. p. 574.

disease, for it assists in removing both foreign material and excessive secretions.

On the other hand, coughing is a useless act when it is caused by an abnormal irritability of the air-passages or by reflexes from other organs; whenever, in fact, it occurs without there being something to be removed. It is then not only useless, but disadvantageous, for coughing greatly increases the intrathoracic pressure, and so interferes with the entrance of the venous blood into the chest cavity. It likewise raises the general arterial pressure. During coughing, therefore, there is danger of rupturing an artery, and the venous flow to the heart is lessened. Coughing also distends the lungs, owing to the increased pulmonary pressure, and a chronic cough may thus lead to a loss of pulmonary elasticity. For all these reasons, coughing *per se* is harmful, and, unless it serves to remove material from the air-passages, it should be controlled so far as possible.

Stenosis of the Air-Passages.—A deficient interchange of gases in the lungs may arise from a stenosis of the air-passages. The results of such narrowings differ materially according to their locations. If the passage through the nose be completely occluded, it may be troublesome at first, but the adult soon learns to breathe through the mouth and to take his food as usual. Not so with the nursing infant. It cannot nurse properly if the nasal passage be closed, and the condition may then be very serious, on account of the interference with the ingestion of food.

A stenosis of the larynx or trachea is much more serious. This may arise, first, from processes which compress the trachea, such as goitres, mediastinal tumors, and aneurisms; and, secondly, from diseases within the air-passages, especially from swellings of the mucous membrane of the larynx. The more narrow the passage, the more easily is it closed by such a swelling, and for this reason a swelling of the glottis in

children is especially dangerous. The manner in which the majority of the forms of stenosis of the larynx produce the obstruction is easily understood, and need not be discussed. Less understood are those forms which begin very suddenly, last for a few minutes or hours, and then as suddenly disappear. To this class belong pseudocroup, spasm of the glottis, and whooping-cough. We believe that there can be no doubt that, in all these conditions, the essential factor is a spasm of the muscles which approximate the vocal cords. In addition, there is, in pseudocroup, an extremely acute inflammation of the mucous membrane, which can be seen under favorable conditions and which persists for hours after the cessation of the paroxysm, being accompanied by the symptoms of cough and hoarseness. In whooping-cough there is, in the great majority of cases, no inflammation of the laryngeal mucous membrane, and the paroxysms are here produced solely by a spasm of the muscles which close the glottis. We do not know exactly what causes this spasm in whooping-cough. So-called spasm of the glottis usually affects rhachitic children, and it is not infrequently associated with enlargement of the thymus gland and with the symptoms of tetany. Here again the cause of the spasm is unknown.

If there is an obstruction to the entrance of air into the lungs, the relative amount and the partial pressure of the carbon dioxide in the alveoli increase, whereas the relative amount and the pressure of the oxygen decrease; so that the interchange of gases with the blood proceeds at a slower rate than normally, and, unless some compensatory mechanism comes into play, the blood leaves the lungs abnormally poor in oxygen and abnormally rich in carbonic oxide.

Stenosis of the trachea or of the larynx leads to changes in the respiratory movements which tend to produce a better aëration of the blood. We know that variations in the gases of the blood act directly upon the respiratory centre, and that

the latter is stimulated both by a lack of oxygen and by an excess of carbon dioxide. It would, however, be beneficial if the respiratory movements were increased even before any actual change in the character of the blood took place; for by this means it might be possible to compensate completely for the hinderance to the entrance of air into the lungs before the body could be harmed. There is reason to believe that this does, indeed, occur. The vagus fibres, which may strengthen both inspiration and expiration, are stimulated by a diminished intra-alveolar pressure. In stenosis of the larger air-passages, a transitory, abnormal, negative pressure is present in the alveoli at the beginning of inspiration, because the air does not enter the chest cavity freely. This negative pressure probably leads to an increase in the inspiratory movements through a stimulation of the vagus nerves. In more advanced stenosis, the gases of the blood are unquestionably altered, and the increase in the carbon dioxide is especially potent in stimulating the respiratory centre and in causing deeper respirations.

If the inspirations become deeper from any cause, the ordinarily inspiratory muscles contract more forcibly, and new groups of muscles become innervated from the respiratory centre. Whenever the air cannot enter the chest cavity readily, a considerable negative pressure prevails there during inspiration, and the softer parts of the thorax are pressed in by the atmospheric pressure without. There results the well-known inspiratory retraction of the epigastrium, of the lateral portions of the chest wall, and of the soft tissues above the sternum and clavicles. This is especially striking in cases of laryngeal stenosis.

The respirations accompanying laryngeal or tracheal stenosis are not only more powerful than normal, but are also of longer duration. We know that when the distention of the lungs has reached a certain limit, expiration is initiated by

a reflex through the vagus nerve. In tracheal stenosis, the air cannot enter the lungs freely. They do not therefore become distended so quickly as in health, the reflex through the vagus is delayed, and inspiration is prolonged. Expiration is likewise lengthened because the air cannot easily escape from the lungs on account of the stenosis.

Normally, expiration is a purely passive act, due to the elastic contraction of both the chest wall and the lungs; but in the conditions under consideration, expiration becomes active, being assisted by the contraction of certain muscles, which tend, on the one hand, to force the diaphragm up, and, on the other, to compress the thorax laterally. In stenosis of the trachea and larynx, therefore, expiration is lengthened, is more powerful, and is converted from a passive into an active process.

This slow respiration of stenosis is directly beneficial to the patient. Experimental work has shown that, if the trachea be artificially narrowed, a slow rate of breathing allows more air to enter and to escape from the lungs than does the ordinary rate under the same conditions.[6] It is true that the extra exertion involved consumes more oxygen, but this is more than neutralized by the greater supply of that gas.

In paralysis of the posterior crico-arytenoid muscles, inspiration alone is interfered with, for it is their function to retract the vocal cords during inspiration. Should they fail to do this, the cords are sucked downward and together as the air enters, and this produces an inspiratory stenosis, even though the passage is perfectly free during expiration. Membranes and polyps which float loosely above the glottis may likewise give rise to an inspiratory dyspnœa, while those below the larynx may produce an opposite effect.

The entrance of air into the alveoli may also be hindered by narrowings of the coarser or finer bronchi. In such cases

[6] Köhler, Arch. f. exp. Path., vol. vii. p. 1.

the results depend entirely upon the site and extent of these narrowings. If the main bronchus on one side be obstructed, then the side in question expands less than the other, the normal respiratory murmurs are diminished on this side, and a stridor, caused by the stenosis, is heard. The breathing may become labored, but usually it does not assume the slow rhythm so characteristic of tracheal stenosis, probably because the respiratory rate is governed by the healthy lung.

When any stenosis develops slowly, the patient learns to husband the oxygen which he receives by carrying out movements with the least possible exertion. In this way a man may work, even though the respiratory capabilities of his lungs have become far less than normal.

The large bronchi may be narrowed by many of the causes which lead to stenosis of the trachea; as, for example, by tumors or cicatrices within, or by tumors or aneurisms pressing upon them from without. On account of the large caliber of these tubes, a swelling of the mucous membrane does not ordinarily obstruct the passage of air. In the case of the smaller bronchi, however, the most frequent cause of obstruction is just such an inflammation of the lining mucous membrane. If only the larger bronchi are involved in a bronchitis, little effect, therefore, is produced upon the interchange of gases in the lungs; whereas, if the smaller tubes become inflamed, the results are far more serious. This is especially true of children, on account of the small size of their air-passages, and is also true of those who have scoliosis, for their pulmonary surface is already reduced from that cause.

In every severe bronchitis the respiratory rate is increased, and sixty or eighty per minute, or even more, is not uncommon. At the same time, the respirations become more shallow. The rate is usually faster when the patient has fever, for fever itself accelerates the breathing. We are quite ignorant as to the cause of the characteristic breathing of bronchitis and

especially of the cause of its shallowness. A mere retention of carbon dioxide in the blood will not produce this effect. Possibly the accumulation of this gas in the pulmonary alveoli, or the inflammation as such, stimulates the vagus endings in some peculiar way; but of this there is no direct proof.

Bronchial Asthma.—The symptoms of bronchial asthma are probably caused by a general narrowing of the bronchi, and they may therefore be discussed in this connection. The violent paroxysms of dyspnœa, which characterize asthma, usually begin at night, independently of circulatory conditions, and usually last hours or days. Inspiration and expiration are both labored, but expiration is especially interfered with. There is usually some cyanosis and inspiratory retraction of the soft tissues about the chest. During the paroxysm, the lungs rapidly increase in volume until they attain their maximum expansion, such as is present normally only on deepest inspiration. Numerous musical râles, caused by the passage of air through the narrowed tubules, are heard over the lungs. In the earlier stages of the disease, the patient usually feels well between the attacks, but later he is apt to suffer from bronchial catarrh, cough, and at times from continual dyspnœa.

Asthma is frequently associated with diseases of the bronchi, especially with that condition described by Curschmann as bronchiolitis exudativa chronica, which is characterized by a tough and mucinous sputum, containing spirals and Charcot-Leyden crystals. The chemical investigation of the asthmatic sputum lends support to the view that it is essentially an anomaly of secretion rather than a true inflammatory exudate.[7] Some believe that asthma may follow the ordinary bronchitis of pulmonary emphysema, but this view is not well substantiated. It is often difficult in these cases to determine whether the emphysema or the asthma is primary; but it

[7] F. Müller, Sitzber. d. Gesell. zur Beför. der ges. Naturwissensch., Marburg, 1896, No. 6.

usually seems to be the latter. Asthmatic attacks have been frequently observed in association with diseases of the nose, such as polyps and swellings of the mucous membrane covering the turbinated bones and the septum. Possibly these nasal conditions are related in some way to the bronchiolitis exudativa. Both may occur and improve together, yet not every case of asthma that is caused by nasal reflexes is accompanied by this peculiar change in the bronchioles. Reflexes from other portions of the respiratory tract, and even from other organs, may precipitate the asthmatic paroxysm, but in the majority of these cases a bronchiolitis exudativa is present.

Since asthma may be produced by such different causes, it seems doubtful if all cases are really of the same nature. In the great majority, a bronchiolitis is present, and these cases, at least, can be grouped together for consideration. As to the cause of the hinderance to the entrance and, especially, to the exit of air, the first theory which suggests itself is that the obstruction is due to the swelling of the mucous membrane and to the abnormal secretion of mucus.[8] It seems to us, however, improbable that these could produce an obstruction so rapidly as it occurs in asthma, and we know, furthermore, that an ordinary catarrh of the finer bronchi produces quite a different clinical picture.

The asthmatic paroxysm seems to be rather of a spasmodic character. Two theories have been advanced as to the location of the asthmatic spasm. According to one, asthma is due to a spasm of the diaphragm, induced by a stimulation of the vagus nerve.[9] Such an explantation would account for the great distention of the lungs, but it leaves unexplained the inspiratory retraction of the soft tissues about the thorax and the presence of the sibilant râles. Furthermore, it is extremely improbable that the diaphragm, a voluntary muscle, should be able to

[8] Ungar, Kongr. f in. Med., 1885, p. 245.
[9] Riegel, ibid , p. 250.

remain in a state of tonic contraction for hours at a time without tiring.

According to the other theory, the spasm affects the muscles of the smaller bronchi; and this seems more probable, for it has been demonstrated experimentally that a spasm of these muscles will give rise to all the symptoms of asthma.[10] In addition to this spasm, there may be present a catarrhal or hyperæmic swelling of the bronchial mucous membrane. It is not yet certain just how great a rôle such spasms of the bronchioles actually play in the production of the asthmatic attacks in man, and just what part may be played by contractions of the diaphragm.

The attacks may certainly be initiated through reflex influences; arising, most frequently, from sensitive parts of the respiratory tract, such as the turbinates of the nose and the surfaces of the finer bronchi. The nature of the primary irritant which gives rise to the reflex and the cause of the increased sensitiveness of the points from which the reflex starts are alike unknown to us. For a long time there was a tendency to regard the Charcot-Leyden crystals of the sputum as the primary irritants, but they have since been found in many other conditions.

Paralysis of the Respiratory Muscles.—The aëration of the lungs suffers if the thorax or the lungs cannot sufficiently expand and contract. A mere rigidity of the chest wall usually does little harm, for, by increasing the movements of the thorax as a whole, and of the diaphragm, the lungs may be moved sufficiently to keep them aërated.

More serious consequences result from weakness of the respiratory muscles. These latter may be affected directly as in general muscular atrophy or trichinosis; or they may be paralyzed in various diseases of the nervous system. The

[10] Gerlach, Pflüger's Arch., vol. xiii. p. 491; Einthoven, ibid., vol. li. p. 367.

diaphragm and the other muscles of respiration may be para-
lyzed together or separately. Extraneous conditions frequently
interfere very seriously with the diaphragmatic movements;
such as, for example, pleurisy, peritonitis, and abdominal dis-
tention, whether from fluid, gas, or a tumor. These latter
conditions interfere with the respiration by forcing the dia-
phragm up and by offering an abnormal resistance to its in-
spiratory descent.

The disturbance of respiratory function from these various
causes is intimately dependent upon the extent and the loca-
tion of the disease. A destruction of all inspiratory muscles
is quickly fatal. Of the more limited diseases, the most dan-
gerous is bilateral paralysis of the diaphragm, which may be
caused by disease of both phrenic nerves. This condition is
also always fatal. A less serious paralysis may not cause
death, but merely interfere with the interchange of gases in
the lungs. The respiratory muscles remaining unparalyzed
are then stimulated to increased exertion, and this may give
rise to some unusual type of respiration, such as a pure costal
type in a man, etc.; and not only the type, but also the rate
of the respirations may be changed.

Loss of Pulmonary Elasticity. Emphysema.—As has
been mentioned already, the elasticity of the lungs plays an
important rôle in normal respiration, for it is one of the main
factors in forcing the air out during expiration. If the lungs
are greatly over-distended, or if their tissue suffers alteration
in certain other ways, then their elasticity—i e., their tendency
to collapse—is more or less lost. Such a loss of elasticity of
the whole or of a part of the lungs may result from many
causes, such as diseases associated with violent inspirations or
coughing, or those in which the exit of air from the lungs is
obstructed. If a large portion of the lungs has lost its elasticity
from over-distention, respiration becomes difficult; for the
distended lung does not exhibit the normal tendency to col-

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lapse on expiration, and, not being fully collapsed, it cannot expand so well on inspiration. For this reason the functional capacity of the inelastic lung remains less than normal, even after the primary cause of the over-distention has ceased to act.

Emphysema of the lungs diminishes the pulmonary elasticity. This is serious, because the emphysema is irreparable and lasts throughout life, and especially because it causes, in addition, an actual loss of lung substance. Many alveolar septa disappear during the disease, and the total functioning surface of the lungs is markedly contracted. The loss of the septa leads to an obliteration of many pulmonary capillaries, and so increases the resistance to the flow of blood through the lungs. For this reason hypertrophy of the right ventricle and accentuation of the second pulmonic sound are common findings in emphysema. Emphysema is usually unevenly distributed throughout the lungs, the free margins in front being most affected.

Emphysema tends especially to develop in those whose pulmonary tissues have been exposed to injuries, such as are produced by asthma and bronchitis. Yet not all patients suffering from these diseases become affected with emphysema; and, furthermore, the condition may develop in individuals who have not apparently been exposed to any injurious agents. There seems, therefore, to be some special abnormality in the lungs of susceptible individuals, which either reduces their resistance to injurious agents, or allows spontaneous degeneration to take place. Whether these abnormalities are of a chemical or of a structural nature is uncertain. Virchow believed that, since the emphysematous portions of a lung are poor in pigment, the disease must have originated in many cases before the fifth year of life.

Emphysema interferes with the interchange of gases in the lungs by decreasing both their elasticity and their func-

tioning respiratory surface. Consequently, the carbon dioxide
escapes less readily from the blood, and, being retained in
the body, it stimulates the respiratory centre in the medulla,
thus causing stronger and perhaps more frequent respirations.
The bronchitis that so often complicates emphysema likewise
tends to accelerate the breathing. The deeper and more fre-
quent respirations may to a certain degree neutralize the ill
effects of the loss of elasticity.

**Respiratory Changes of Nervous Origin. The Cheyne-
Stokes Phenomenon.**—Changes in the activity of the respira-
tory centre may directly influence the amounts of air which
pass in and out of the lungs. Thus, when the intracranial
pressure is increased, the respirations usually become slower
and deeper, and frequently also more irregular. Anatomical
lesions that injure, without destroying, the respiratory centre
may give rise to similar effects.

The peculiar type of breathing known as the Cheyne-
Stokes respiration may be considered in this place.[11] In this
condition the respiratory rhythm is broken by pauses of apnœa.
After one of these pauses, the respirations are at first weak
and superficial, but gradually they become stronger and
stronger, until they are exceedingly labored. Following this
extreme dyspnœa, the respirations gradually diminish in
strength until they cease altogether in the period of apnœa,
and the cycle of events is completed. Nervous symptoms
frequently accompany the respiratory changes. The patient
may lie in a stupor during the apnœa, to awake during the
period of dyspnœa with oppressive sensations. The pupils
may be contracted and reactionless during the apnœa, but
become dilated and mobile during the dyspnœa. According
to Traube, the pulse usually remains unaffected by the varia-

[11] Traube, Beitr., ii. p. 882 and iii. p. 103; Sokolow and Luchinger,
Pflüger's Arch, vol. xxiii. p. 283; Löwit, Prag. med. Wochens., 1880, Nos.
47–50; Unverricht, Kongr. f. in. Med., 1892, p. 399.

tions in the breathing, though it may show definite changes in frequency and tension. Of the various causes which may produce a Cheyne-Stokes type of respiration, the most important are uræmia and diseases of the brain and heart.

The cause of this symptom-complex is believed to be some change in the irritability of the respiratory centre. Filehne [12] held that Cheyne-Stokes breathing is due to a relative insensitiveness of this centre to the action of venous blood. For this reason the accumulation of carbon dioxide in the body does not affect the respiratory centre readily, and it is only after the venous blood has stimulated the vasomotor centre, and so has caused a constriction of the arteries leading to the brain, that the respiratory centre is finally influenced by the small amount and poor quality of the blood which it receives. The breathing then gradually deepens, and the blood becomes better aërated. The vasomotor centre, being no longer stimulated by venous blood, allows the arteries to dilate, and thus a fresh supply of arterial blood reaches the respiratory centre. The latter is then no longer stimulated by an insufficient blood-supply, and the animal stops breathing. Thus the cycle is completed and a new one can begin. This theory has been sharply attacked, especially by Rosenbach, who believes that the venous quality of the blood does not cause the Cheyne-Stokes phenomenon.[13] It is impossible to discuss the various explanations given for this type of breathing, mainly because so few facts are known to us. It should, however, be remembered that even in healthy individuals there is a tendency to periodic breathing, which is most marked during sleep, and that many animals always show this type of respiration. Of special interest is the theory of Unverricht,[14]

[12] Arch. f. exp. Path., vol. x. p. 442, and vol. xi. p. 45; Ztft. f. klin. Med., vol. ii. p. 255.

[13] Ztft. f. klin. Med., vol. i. p. 583, and vol. ii. p. 713.

[14] Kongr. f. in. Med., 1892, p. 399.

who held that the phenomenon is due to some disturbance in the nervous paths connecting the cortex and the respiratory centre in the medulla.

Changes in the respiratory centre are probably responsible for the abnormal breathing seen in certain intoxications; such, for example, as the spasmodic breathing of hydrocyanic acid poisoning, or the deep respirations of diabetes, uræmia, and other conditions.[15] The frequent and superficial respirations of salicylic acid poisoning and the various forms of dyspnœa which may be present in hysteria also seem to be due to nervous influences.

The respiratory centre may be affected by reflexes from various parts of the body, especially from the abdominal organs. The conditions known as asthma dyspepticum,[16] asthma uterinum, etc., are caused in this manner.

Pleural Effusions and Pneumothorax.—Even though the movements of the chest are normal, and the air can reach the alveoli, respiratory difficulties may arise from a diminution of the total functionating pulmonary surface. Such a diminution may be caused by numerous diseases, either because they fill the alveoli with inflammatory products, as happens in pneumonia, or because they obliterate them by pressure from without, as happens in large pleural exudates.

When fluid collects in the pleural cavity, the lung at first retracts in virtue of its elasticity, but later it is pressed upon by the fluid, and it may be entirely emptied of air by very large effusions. A pleural effusion does harm in several ways. In the first place, the retraction and compression of the lung on the side of the fluid naturally diminishes the surface available for the interchange of gases. Since the pressure in the diseased pleural cavity is higher than that in the healthy cavity,

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[15] Kussmaul, Arch. f klin. Med., vol. xiv. p. 1; Senator, Ztft. f. klin. Med., vol. vii. p. 235.

[16] Boas, Arch. f. Verdauungstr., vol. ii. p. 345.

the fluid tends to force the mediastinum toward the healthy side, and so to interfere not only with the function of the lung on the affected side, but with that on the healthy side as well. A pleural effusion also influences the circulation of the blood. The negative pressure, normally present in the thorax, is diminished, and the venous flow from the periphery toward the heart is consequently retarded. Large exudates may even compress or kink the inferior vena cava. The increased pressure upon the capillaries of the lungs raises the resistance in the pulmonary circulation, and thus increases the work of the right ventricle.

If air escape into the pleural cavity through a wound in the chest wall, or through an opening in a lung produced by such causes as tuberculosis, abscess, gangrene, or injury, it gives rise to many of the same results as does an effusion. When such a pneumothorax communicates freely with the external air, the pressure in the affected cavity will be the atmospheric pressure. If, however, the opening becomes completely closed, then a part of the air in the pleural cavity is absorbed, and the pressure in this cavity, though less than that of the atmosphere, remains greater than that on the normal side. If, finally, the opening be of a valvular nature, such that it will permit air to enter the pleural cavity, but will prevent its exit, then the pressure within will exceed the atmospheric pressure, at least during rest and expiration, and not only the lung of the affected side, but that of the other side also, will be subjected to considerable pressure.

The seriousness of a pneumothorax depends mainly upon the functional capacity of the healthy lung. If this can functionate without interference, all the demands of the resting body may be met, even though the pneumothorax should have developed suddenly. Unfortunately, the healthy lung is often encroached upon by the mediastinum, owing to the fact that the latter is thrust past the median line by the high

pressure in the affected cavity.[17]   When the opening into
the pleural cavity is a large one, and admits of free commu-
nication with the external air, then with each inspiration the
mediastinum is displayed toward the healthy side, and the
air does not enter the normal lung so well as normally.   Less
effect is produced if the mediastinum is very rigid or if the
opening into the pleural cavity is a small one.   The severe
collapse which sometimes follows a large perforation into the
pleural cavity, may be overcome experimentally by preventing
this displacement of the mediastinum.   In general, a right-
sided pneumothorax is more serious than a left-sided one,
because of the greater capacity of the right lung.

Atelectasis.—An inflammation of the smaller bronchi may
decrease the respiratory surface of the lungs, for when the
bronchioles are occluded by a swelling of the mucous mem-
brane, the corresponding alveoli are rendered useless.   If the
occlusion persists for a long time, the air contained in the
affected air cells gradually undergoes absorption and the cor-
responding pulmonary tissues become atelectatic.[18]   The oxy-
gen and carbonic acid gas are rapidly absorbed, the nitrogen
more slowly.   The gases are absorbed because the alveoli tend
to contract, and in this manner they keep the partial pressure
of the various gases within them at a higher level than the
partial pressure of these same gases in the blood.

Atelectasis may also be caused by compression of the lungs,
as from large pleural effusions or pneumothorax.   According
to Lichtheim, it is possible for the alveoli to become atelectatic,
even though there is no occlusion of the bronchi and no actual
compression.   For example, the portion of the lung which
dips into the fluid of a small pleural exudate is not subjected
to a positive pressure, and yet it is usually found to be free
of air.

[17] See Garre-Quincke, Grundriss der Lungenchirurgie, Jena, 1903, p. 40.
[18] Lichtheim, Arch. f. exp. Path., vol x. p. 54.

The Effects of an Obliteration of the Air-Spaces.—The disturbances produced by a diminution of the functioning surface of the lungs depend upon several factors, such as the amount of pulmonary tissue thrown out of function, the rapidity with which this occurs, the demands of the body for fresh oxygen, and the degree to which an increase in the respiratory movements can compensate for the loss of functioning tissue.

Such a diminution in the functional capacity of the lungs always causes a deepening of the respirations, and frequently an increase in their rate as well. The latter is especially marked when fever is present, for the heated blood seems to stimulate the respiratory centre not only directly, but through reflexes from the skin. Even though there be no fever, the respirations may be accelerated. One probable cause for the increased respiratory movements in these conditions is the stimulation of the respiratory centre by the carbon dioxide retained in the blood, though it must be admitted that we possess no positive data actually proving that such a retention takes place in cases of atelectasis. The breathing may also be accelerated from another cause. The inspiratory movements enlarge the chest cavity, and, since many alveoli involved in the atelectasis do not expand, the remaining ones must expand all the more. This excessive distention of certain alveoli probably stimulates the vagus nerve, thus rendering the succeeding expiration prompt and forcible, and perhaps increasing the respiratory rate. This is a possible explanation of the rapid respirations so frequently seen in cases of atelectasis without fever.

Disturbances in the interchange of gases in the lungs may arise from changes in the chemical or physical character of the alveolar membranes. Of this we have no direct experimental proof, but *a priori* it would seem possible, and the dyspnœa of patients who suffer from chronic passive conges-

tion, consecutive to heart disease, is partially accounted for by changes in the alveolar epithelium.

The Effects of Atmospheric Pressure upon Respiration.— Variations in the composition of the air must produce certain effects upon the animal organism, for the passage of the gases through the alveolar membranes depends primarily upon the relation existing between the partial pressures of these gases in the blood and in the air-cells. The partial pressure of oxygen in the lungs may be diminished either by diminishing the atmospheric pressure as a whole or by diminishing the relative proportion of oxygen in ordinary air. Practically, the latter is seen only when an animal is allowed to breathe in a small air-tight space until the oxygen is reduced. The symptoms produced are those of asphyxia, and will be spoken of in that connection (p. 225).

The effects of low atmospheric pressure are frequently seen,[19] especially in those who make balloon ascensions and in those who reach great heights in mountain climbing. The symptoms may be merely unpleasant at first, but at higher elevations they become actually dangerous. The height at which symptoms develop varies for different individuals and under different conditions. Dyspnœa, headache, prostration, paralysis of the extremities, and finally complete unconsciousness are among the symptoms which may appear during a balloon ascension, and a similar set of symptoms—viz., fatigue, headache, sleepiness, palpitation, nausea, rapid pulse and respiration, and especially dyspnœa—may also harass those who ascend high mountains. In both instances the symptoms are not caused by the reduction of atmospheric pressure alone, but are due in part to the cold, the wind, the dazzling light, and the bodily and mental strain. Unquestionably, however, the rarefied air is the main cause of the disturbances, even in

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[19] Miescher, Arch. f. exp. Path., vol. xxxix. p. 464; Kronecker, Die Bergkrankheit, Berlin, 1903.

mountain climbing, for the symptoms can appear in persons who do not climb but are carried up the mountain.[20]

A considerable rarefaction of the respired air may take place without any resulting disturbance in the interchange of gases in the lungs. Most animals and men will endure, without serious consequences, a reduction of the atmospheric pressure from the normal of 760 mm. down to 450 or 400 mm. of mercury, and some will stand a reduction to half an atmosphere or less. The manner in which the individual breathes is of great importance in determining his ability to withstand these reductions of pressure. Those that are accustomed to keep their lungs well ventilated with fresh air resist a lowering of pressure comparatively well, for they know how to keep the partial pressure of oxygen in their alveoli at a relatively high level. Anything that acts unfavorably upon the mechanics of respiration, such as cold, wind, loss of sleep, etc., renders the individual more susceptible to a diminution in atmospheric pressure. For these reasons there are great individual variations in the ability to withstand low atmospheric pressures, and animals, as well as men, living at high altitudes gradually learn to breathe in such a manner that the partial pressure of the oxygen in their alveoli shall be maintained at a comparatively high level.

According to certain observers,[21] the interchange of gases in the lungs is not affected until the pressure of the external air reaches about half an atmosphere. If the pressure be reduced beyond this, then the elimination of carbon dioxide is markedly increased and the absorption of oxygen is likewise somewhat increased, though relatively less so, at least in the early stages. Observations by Zuntz, extending over several

[20] Egli-Sinclair, Wien. med. Blätter, 1895, 8 and 9.

[21] Fraenkel and Geppert, Ueber die Wirkungen d. verdünn. Luft auf d. Organismus, Berlin; Loewy, Unters. ü. Resp. u. Circ., etc., Berlin, 1895.

weeks, upon persons at the top of Monta Rosa (four thousand
five hundred metres high), showed a considerable increase in
the respiratory movements and in the consumption of oxy-
gen, though the amount of this increase differed in differ-
ent individuals. The persons subjected to these last experi-
ments did not seem to become acclimated to the changed
conditions within the short time that they remained at the
high altitude.

The oxygen-carrying capacity of the hæmoglobin does not
diminish at the same rate as does the partial pressure of the
oxygen to which it is exposed. Thus Hüfner [22] has shown
that with the partial pressure of oxygen at 124 mm. (corre-
sponding to an elevation of two thousand metres), ninety
per cent. of the hæmoglobin remains undecomposed, at a
partial pressure corresponding to an elevation of four thousand
metres, eighty-eight per cent., and at one corresponding to six
thousand metres, eighty-five per cent., remain undecomposed.
The dissociation of oxyhæmoglobin may therefore be rela-
tively slight at these high altitudes, and it is to this fact that
the animal body owes its considerable ability to resist reduc-
tions of pressure. Yet we must remember that the partial
pressure of the oxygen in the lungs may be considerably lower
than is its partial pressure in the outside air. As the blood
becomes insufficiently aërated, the respiratory movements are
increased and the partial pressure of the oxygen in the alveoli
is raised. This constitutes a most important mechanism,
whereby the body is able to compensate for reductions of
atmospheric pressure. Muscular exercise sometimes relieves
the unpleasant symptoms of a rarefied atmosphere, probably
because it stimulates the respiratory movements.

In conclusion, we may say that the effects of a high altitude
are caused mainly by the diminution in the tension of the
oxygen, and to a lesser extent by other causes. The condi-

[22] Englemann's Arch , 1901, p. 187.

tions are very complicated, and it must be acknowledged [23] that various factors, such as circulatory disturbances, for example, may contribute to the production of symptoms. Yet, in my opinion, the lack of oxygen is the essential cause, and this view is supported especially by the fact that the symptoms of those who ascend to great elevations in balloons are often promptly relieved by inhalations of oxygen.

Increasing the density of the air even up to twice the normal pressure is, according to recent observations,[24] without any effect upon the " quality or quantity" of the respiratory interchange of gases. The increased appetite and the loss of weight that are seen in persons subjected to high pressures cannot therefore be accounted for by any anomalies in the respiration.

The Inhalation of Poisonous Gases.—The respired air may contain substances which are poisonous to the body. A certain protection from these poisonous admixtures is furnished by our sense of smell, and some gases, such as ammonia and sulphuretted hydrogen, are avoided on account of their odors. Yet the odor of hydrocyanic acid may be perceived only after it is too late to escape its deadly action.

Carbon monoxide, as usually inhaled, is mixed with gases which possess an odor. Poisoning from this gas is of especial interest, on account of the marked affinity which it possesses for hæmoglobin.[25] When the air contains about one part in a thousand of carbon monoxide, the latter passes into the blood, where it unites with a portion of the hæmoglobin in such a manner that this latter can no longer combine with oxygen to form oxyhæmoglobin. If only a small amount of hæmoglobin is thus thrown out of function, no serious damage

[23] Kronecker, Die Bergkrankheit, Berlin, 1903.

[24] Loewy, loc. cit.

[25] Hüfner, Arch. f. exp. Path., vol. xlviii. p. 87; Mosso, Die Atmung in d. Tunnels u. d. Wirkunk d. Kohlenoxyds, see Jahresbcr. f. Tierchemie, vol. xxx. p. 576.

results, and the patient has only a few symptoms, such as headache, etc. If he then breathes good air, the changed hæmoglobin is either excreted, or the combination between it and the carbon monoxide is gradually decomposed by the mass action of fresh oxygen. When, however, large quantities of hæmoglobin are thus thrown out of function, the blood can no longer furnish the necessary oxygen to the body.[26] Under such circumstances, the carbon dioxide is excreted through the lungs as usual, but the supply of oxygen is diminished, and this becomes dangerous as soon as about fifty per cent. of the total hæmoglobin is decomposed. In rabbits killed by carbon monoxide only twenty to thirty per cent. of the normal amount of oxygen was found in the blood at the time of death. Part of the carbon monoxide in the blood passes into the tissues, and there exerts its anæsthetic action. Consequently the respirations early become paralyzed, and the clinical picture presented differs entirely from that of acute asphyxia. If the poisoned person be removed from the gas, and if he breathe ordinary air, or, better still, pure oxygen, then the combination between the carbon monoxide and the hæmoblobin is gradually decomposed and he may be saved.[27]

The Effects of Anæmia upon Respiration.—The supply of oxygen to the tissues may be influenced by a reduction of hæmoglobin. If there be too small a quantity of this pigment in the circulating blood, or if that present be transformed into some useless modification, such as the carbon monoxide compound or methæmoglobin, then the supply of oxygen to the body may become insufficient. In an acute hemorrhage death results from this cause when about seventy per cent. of the total quanity of hæmoglobin is lost.

If the loss of hæmoglobin or of blood be very gradual, then the body learns to accustom itself to the changed conditions,

[26] Dreser, Arch f. exp Path., vol. xxix p. 119.
[27] Gréhant, compt rend., vol. cii p 825

and a much greater reduction can take place. We do not know the limits to which such a gradual reduction of the total hæmoglobin may go, for we have no method for accurately determining the total quantity of blood in the body. Nor do we fully understand the manner in which the body accommodates itself to a gradual loss of hæmoglobin. It is certain that there is no modification of the hæmoglobin itself in these cases, whereby it is enabled to transport larger quantities of oxygen.[28] Furthermore, the total amount of oxygen absorbed and of carbon dioxide eliminated during rest are little if any below the normal limits, even though the anæmia be severe.[29] Such patients learn to restrict their movements as much as possible, and so to lessen their need for oxygen; and although the quantity of oxygen which they consume during rest is the same as that used by a healthy individual, yet their gaseous interchange during exercise is much less than normal.[30] Then it is that their lessened facilities for transporting oxygen are most noticeable, and every physician knows how incapable of exertion these anæmic persons are.

Since in an anæmic person a small amount of hæmoglobin must supply the tissues with the usual amount of oxygen, at least during rest, it follows that either the hæmoglobin present makes more frequent journeys from the lungs to the tissues, or that it gives up more oxygen to the tissues at each journey. We possess no evidence proving that the blood flow is increased in anæmia, though the rapid heart action so frequently observed does perhaps tend to produce this result. It is much more probable that the oxyhæmoglobin of the blood is more reduced in the tissues of an anæmic than in those of a healthy

[28] Hüfner, Englemann's Arch., 1900, p. 39; ibid., 1903, p. 217.

[29] Pettenkofer and Voit, Ztft. f. Biol., vol. v. p. 419; Pembry and Gurber, Jour. of Physiol., vol. xv. p. 449; Thiele and Nehring, Ztft. f. klin. Med., vol. xxx. p. 41.

[30] Kraus, Ztft. f. klin. Med, vol. xxii. pp. 449, 574.

individual, and that, correspondingly, a given amount of hæmoglobin must take up relatively more oxygen in the lungs. The absorption of oxygen from the alveoli is favored by the fact that anæmic persons, by virtue of their increased respiratory movements, usually keep their lungs better aërated than do normal individuals. Consequently the partial pressure of the oxygen in the blood of anæmic persons, though less than the normal, is yet sufficient to meet the needs of the body.

The Effect of Circulatory Changes upon the Respiration. —If the body is to receive a proper supply of oxygen, it is not only necessary that there should be sufficient air in the lungs and sufficient hæmoglobin in the blood, but there must also be a sufficiently rapid blood-stream. The hæmoglobin takes up the oxygen from alveolar spaces very rapidly, and no advantage, therefore, is derived from a slowing of the blood-current through the lungs. When, however, the rapidity of the blood-current is so diminished that the respiratory centre is not sufficiently aërated, then the cells in the medulla are stimulated and the respiratory movements are deepened. These increased respiratory movements are of special value in circulatory disturbances because they not only maintain the partial pressure of the oxygen in the alveoli at a higher level, but they directly assist the flow of blood.

Respiratory Compensation.—We see, therefore, that conditions which injure the external respiration call into play compensatory processes by means of which the body endeavors to protect itself against the harmful effects of a lessened internal respiration. To what extent it is possible to do this depends upon various factors. In the first place, it depends upon the degree to which the external respiration is disturbed, and it is clear, for example, that no compensation can possibly help a patient if an aortic aneurism ruptures and fills all the alveoli of his lungs with blood. Secondly, it depends upon the functional capacity of the compensatory organs, and a

movable chest wall, good muscles, and a powerful heart are most important aids to compensation. Thirdly, it depends upon the respiratory needs of the body. Compensation is more easily maintained when the body is at rest than when the demand for oxygen is increased by exercise or during digestion. Finally, the rapidity of the changes is important and compensation is more easily established when the damage develops gradually; for persons with disturbances of respiration learn in time to minimize their need of oxygen. We have already mentioned the manner whereby the interchange of gases is approximated to the normal in anæmia. The same has also been studied in certain other pathological conditions. It has been shown, for example, that in rabbits a pleuritic exudate or a closed pneumothorax of moderate grade does not influence to any marked degree the quantity of oxygen absorbed or that of carbon dioxide eliminated by the lungs.[31] An open pneumothorax of one side produces equally little disturbance in rabbits and dogs.[32] In man, also, the effect of various diseases upon the interchange of gases has been studied by accurate methods. In emphysema, bronchitis, tuberculosis, pneumonia, and pleurisy, even when marked dyspnœa was present, the interchange between the lungs and the external air was found to be approximately normal. Yet when there is dyspnœa, additional oxygen is used up by the increased respiratory movements; and, if this were deducted from the total amount of oxygen consumed by such patients, there might prove after all to be some reduction in their interchange of gases. The latter seems all the more probable from the fact that the respiratory interchange of gases in the above conditions tends to diminish as the hinderance to the entrance of air increases.

Yet even though the external respiration were apparently unaffected, we must be careful not to assume that the respira-

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[31] Thoma and Weil, Virch. Arch., vol. lxxv. p. 483.
[32] Sackur, Ztft. f. klin. Med., vol. xxix. p. 25.

tory processes within the body are normal; for it is possible
that the tension of the oxygen in the blood might be abnor-
mally low or that of the carbon dioxide abnormally high.
Either would influence the interchange of gases between the
blood and the tissues. Indeed, dyspnœa is usually caused by
just such changes in the blood going to the medulla.

Asphyxia.—When disturbances of external respiration be-
come considerably greater than can be met by the compen-
satory mechanism, asphyxia is produced. The symptoms of
asphyxia vary according to the rapidity of its onset, being
milder and less characteristic in gradually progressive cases.
The blood is altered in two particulars in asphyxia, there being,
first, a diminution in quantity of oxygen present, and secondly,
an increase in the carbonic acid gas. The latter possesses some
anæsthetic action, and consequently, when it acts over a long
period of time, as in chronic asphyxia, the irritability of the
medulla gradually becomes diminished and the respirations
may weaken until life is extinct. In such conditions the effects
of the lack of oxygen do not become apparent, because the
respiratory centre has been narcotized by the carbon dioxide.

Acute asphyxia is produced by suddenly cutting off the
oxygen supply to a brain which has not yet lost its irrita-
bility. Practically, this does not happen very often, but may
result from a filling of the lungs with fluid, from the collapse
of a diseased trachea, or from a rapidly fatal hemorrhage.
The lack of oxygen first causes a deepening and strengthening
of the respirations, followed by characteristic changes in the
circulation. The vasomotor centre is powerfully stimulated,
and this causes the splanchnic vessels to contract, the vessels
of the skin to dilate, and the general arterial pressure to be
markedly raised. The vagus is also stimulated and the heart-
rate is slowed. These changes result in a maximum amount
of blood being sent to the brain so that the latter receives the
best oxygen supply possible. In the later stages of acute

asphyxia generalized tonic and clonic convulsions occur, and finally, after a brief period of paralysis, death supervenes.

The Internal Respiration.—The internal respiration has already been mentioned, and we have attempted to show how changes in the internal respiration of the respiratory centre may cause a compensatory increase in the movements of the chest.

The effect of disturbances of the external respiration upon the interchange of gases in other tissues remains to be considered. The need of the cells for oxygen is determined primarily by their functional activity, yet it must not be forgotten that they cannot use all the oxygen they need unless it is properly furnished to them. It is, indeed, true that for a certain period of time the cells are able to do without fresh air, for the reason that they possess a supply of intramolecular oxygen; but this fact is of little practical importance.

Normally the blood carries much more oxygen than is needed by the tissues, and when it leaves them its supply is by no means exhausted. We have evidence that this excess of oxygen is not a useless luxury, but that it is beneficial, and that a relative scarcity of the gas in the tissues is directly harmful. At least, it has been shown that in dyspnœic dogs the proteid decomposition is increased,[33] and, although the same has not been proved for man, it suggests the harm which may result from an insufficient aëration of the blood. It has been shown also that glucose and lactic acid may appear in the urine of dyspnœic animals, and that lactic acid may be present in the urine of dyspnœic men.[34] Finally, the ratio between the carbonic acid gas eliminated and the oxygen absorbed becomes greater than the normal ratio if the oxygen supply is restricted. Though the explanation of these various findings is uncertain, they serve to show that a diminished tension of

[33] Fraenkel, Virch. Arch., vol. lxvii. p. 273.
[34] Araki, Ztft. f. phys. Chem., vol. xv. p. 335.

oxygen in the tissues leads to pathological changes in the metabolism of the body.

In order to estimate the oxygen supply to the tissues, it is necessary to know the amount of this gas in the blood. Unfortunately, we possess but little information bearing directly upon this point. In animals with an open pneumothorax the quantity of oxygen is much diminished in the arterial blood, and it is this diminution that stimulates the medullary centres, causing such powerful respirations that one lung is able to do the work of two.[35] In the anæmias, also, the total amount of oxygen in the blood is reduced proportionally to the reduction in hæmoglobin.[36] We possess no other data as to the gases in the blood in respiratory diseases. The mere fact that the external interchange of gases with the air does not vary from the normal proves nothing, for this might be the same even though the absolute amount in the blood varied greatly, as, indeed, probably happens in anæmia and pneumothorax. The simple inspection of many patients with respiratory diseases would lead one to the belief that their blood is poor in oxygen, because of the cyanosis present; and yet their consumption of oxygen is known to be approximately normal.

If the oxygen in the blood is diminished, it is supplied to the tissue cells at an abnormally low tension. The amount of carbon dioxide in cyanotic blood is increased, and this will also produce some effect, for even in great dilution it stimulates the respiratory centre.

Even though the lungs be normal, the internal respiration may be affected through changes in the parenchyma cells or in the tissue fluids. A retarded blood-flow or a lack of functioning hæmoglobin interferes not only with the interchange of gases in the lungs, but likewise with the interchange in the

[35] Sackur, Ztft. f. klin. Med , vol. xxix p. 25.
[36] Kossler and Scholz, Kongr. f. in. Med , 1899, p. 378; Arch. f. exp. Path., vol. xlii. p. 323.

tissues. The slowing of the pulmonary blood-stream is of no advantage, for the red cells quickly become saturated with oxygen. The tissues may indeed abstract more oxygen from slowly moving blood, but this must be done under a lower mean pressure, and there is a limit beyond which the slowing of the current cannot go without reducing the oxygen supply to the tissues.

Disturbances in the internal respiration may also be of a local nature, as when arteriosclerotic changes, thrombosis, or embolism interfere with the circulation of a limited portion of the body. If the cerebral arteries are blocked, the resulting anæmia of the brain produces the symptoms of acute asphyxia.

The transportation of carbon dioxide may be interfered with by changes in the blood, especially those produced by an acid intoxication. The additional acid in such intoxications is partly neutralized by an increased formation of ammonia (see p. 337), yet not altogether so, and some of the fixed alkalies of the blood are bound by the extra acid. This diminishes the free alkali in the blood which is available for carbon dioxide transportation, and, in rabbits, at least, the amount of carbon dioxide in the blood may be reduced from the normal twenty-five per cent. by volume, down to two per cent. as the result of an acid intoxication.[37] Under such circumstances, the plasma quickly becomes saturated with carbonic acid gas, and some of the latter is left to accumulate in the tissues. In the acid intoxication of rabbits, the oxidations in the body are also considerably diminished,[38] for the absorption of oxygen from the respired air is less than normal. Since the amount of oxygen in the blood is not lessened,[39] the decrease in the oxidative processes of the body must be referred to changes

[37] Walter, Arch. f. exp. Path., vol. vii. p. 148; H. Meyer, ibid., vol. xiv. p. 313.
[38] Chvostek, Ztrbl. f. klin. Med., vol. xiv. p. 329.
[39] Walter, loc. cit.

in the cells, induced, perhaps, by the toxic action of the re-
tained carbon dioxide. Thus we see that in the acid intoxi-
cation of rabbits the reduction of the fixed alkalies of the blood
leads to disturbances both of internal and of external respi-
ration. To what extent these results are applicable to the acid
intoxications seen in man is not definitely known, for numer-
ous other factors here present complicate the simple picture.

The internal respiration may finally be altered by changes
in the parenchyma cells, either physiological, such as by rest
and activity, by cold and heat, or pathological, as by the
various metabolic diseases. In phosphorus and hydrocyanic
acid poisoning many cells lose to a greater or less extent their
ability to take up oxygen and to form carbon dioxide. Though
the external breathing and the gases of the blood are both
normal, nevertheless the interchange of gases in the tissues
is much diminished, because the cells are poisoned. The animal
dies of internal asphyxia; and in hydrocyanic acid poisoning
the most marked respiratory convulsive movements may result
from this asphyxia of the respiratory centre.

Respiratory Sensations.—The most important pathologi-
cal sensation associated with respiration is that known as
dyspnœa. The term has been used by some to designate dis-
turbances in the respiratory act itself, but we prefer to limit its
use to the subjective sensation of an air-hunger. Such a
sensation is always produced by an insufficient interchange of
gases in the tissues, especially by a diminution in the supply
of oxygen to certain parts of the brain. The retention of
carbon dioxide which is so frequently associated with the
lack of oxygen does not apparently cause this sensation of air-
hunger, for it may be breathed in large quantities without any
such effect. Frequently the respiratory movements are in-
creased without any sensations of dyspnœa, and it would seem
that in such cases a retention of carbon dioxide is the important
factor in producing the more marked respiratory movements.

How the oxygen is prevented from reaching the brain is immaterial, so far as dyspnœa is concerned; the respiratory surface of the lungs may be diminished, the blood may flow slowly, or, finally, either the red corpuscles or the tissue-cells may have lost their ability to take up the oxygen. The need for oxygen is increased by a functional activity of the cells of the body, and for this reason many patients are free from dyspnœa so long as they are quiet, but suffer from it so soon as they exert themselves. Many gradually learn to accomplish their tasks with a minimum expenditure of energy, and so to reduce their need of oxygen and their dyspnœa.

Actual pain may be caused by diseases of the respiratory apparatus. Most authors believe that the lungs themselves contain no fibres which are capable of transmitting sensations of pain and that all pulmonary pains arise from the pleura or the chest wall. Severe pains are frequently present in dry pleurisies, and, since the latter often accompany diseases of the lungs, it is possible that they are responsible for the pain present in many of these cases. Yet the question is not, to my mind, fully settled, for pain may be present in diseases of the lungs which are not accompanied by pleurisy.

CHAPTER VI.

THE DIGESTION.

The Mouth and Œsophagus.—Digestion includes all of the processes which assist in preparing the food for use in the body. Disturbances of digestion, therefore, begin in the mouth. Here the food is seized by the teeth and is ground up so that it shall present a greater surface to the action of the digestive juices. Serious disturbances may follow improper trituration of the food, whether this results from diseases of the teeth, the maxilary bones, or the temporo-maxillary joints, or from weakness of the muscles which move the food about within the mouth. If the facial nerves are paralyzed, the food collects in the cheeks and cannot be forced back into the mouth. A paralysis of the tongue interferes not only with chewing, but with the passage of food into the throat. When chewing becomes a painful procedure, malnutrition may be a consequence; for many patients with ulcerations in the mouth, or with inflammations of the tonsils, throat, or parotid glands, would rather suffer from hunger than from the pain which is caused by the taking of food. The intensity and the duration of such diseases both influence the amount of disturbance which they produce.

Stomatitis.—The causes of stomatitis are various. If particles of food are retained in the mouth, they decompose, and the products of decomposition, acting as irritants, may pave the way for the invasion of micro-organisms. Inflammations are also more liable to occur when the growth of bacteria is favored by carious teeth, or when, as the result of severe illnesses, but little saliva is secreted and the mouth is allowed to become foul owing to the stuporous condition of the patient. The stomatitis which so often accompanies severe diabetes is

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greatly favored by the caries of the teeth and by the organic acids, both of which are frequently present in the mouths of these patients. The oidium of thrush produces acids, and these undoubtedly irritate the mucous membrane directly, and favor secondary infections. Acids and alkalies introduced into the mouth may destroy its coverings and so cause inflammations. The stomatitis of mercurial poisoning is apparently due to the action of the mercurial compounds which are excreted in the saliva. The stomatitis of scurvy seems to be of a different character from that caused by other infectious diseases, for it develops early in the disease and is particularly severe. The scorbutic gingivitis appears to be a specific effect of the disease, though its true cause is as little understood as is the cause of the other scorbutic manifestations.

Stomatitis endangers the health of the patient, first, by diminishing the ingestion of food, which diminution results partly from the tenderness of the mucous membrane, and partly from the loss of appetite caused by the disagreeable taste in the mouth. In the second place, the number of bacteria in the mouth are enormously increased, and vast numbers are swallowed. The ability of the stomach to disinfect this material is limited, its disinfecting power being often most reduced in the very diseases with which the stomatitis is associated. The passage of large numbers of bacteria from the stomach into the intestines may there give rise to abnormal fermentative and putrefactive processes, and may even favor a general infection.

Diminished Secretion of Saliva.—The quantity of saliva is diminished in certain infectious diseases, such as pneumonia and typhoid fever; in certain poisonings, as by atropine; in all diseases which are accompanied by great losses of water, such as cholera, diabetes, and interstitial nephritis; and, finally, in those paralyses of the facial nerve that involve the chorda tympani. A diminution of the saliva is always accompanied by a reduction in the activity of the buccal mucous glands.

The resulting dryness of the mouth not only interferes with the cleansing of the mouth, but also with the acts of chewing, swallowing, and speaking.

To what degree a lack of ptyalin is injurious has not been definitely settled. It was formerly considered that this ferment played an insignificant part in the process of digestion, but we now know that large quantities of starch are converted into dextrin in the mouth and in the stomach by the action of this ferment.[1] The conversion continues in the stomach even after a considerable grade of acidity is present.

Ptyalism.—An increase in the secretion of saliva, so-called ptyalism, may result from an irritation of the chorda tympani nerve as it passes through the middle ear. Impressionable persons frequently have a marked flow of saliva when they think about food or even when they imagine that they have taken calomel. Ptyalism also accompanies all irritative conditions of the mucous membrane of the mouth, such as may result, for example, from stomatitis. The ptyalism of mercurial poisoning is due in all probability to a central or peripheral stimulation of the nervous connections of the salivary glands.[2] It is possible also that the parenchyma cells are directly affected by the poison. Mercurial stomatitis usually follows the ptyalism, and is due to some irritating mercurial compound present in the saliva. This stomatitis will, in turn, increase the salivation, thus establishing a vicious circle.

There is a remarkable increase in the amount of saliva in certain chronic diseases of the medulla oblongata, particularly in bulbar paralysis.[3] This has been compared by some authors to the paralytic secretion which appears in animals after all the salivary nerves have been cut. The latter begins about

[1] J. Muller, Kongr. f. in Med, 1901, p 321
[2] v Mering, Arch. f. exp. Path, vol xiii p 86.
[3] Kayser, Arch f klin. Med, vol. xix. p 145; Kussmaul, Volkmann's Vortrage. No. 54.

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twenty-four hours after the operation, lasts about one week, and gradually ceases on account of the degeneration of the secreting cells. The two conditions differ, however, in the length of time over which the salivation lasts and in the amount of saliva secreted, the quantity being much greater in the case of bulbar paralysis. It seems to me very probable that the ptyalism of bulbar paralysis is not a paralytic secretion, but that it is due to an irritation of the cells of the medulla, which occurs as they degenerate. It is, therefore, comparable to the fibrillary muscular twitchings so often seen when the large motor cells of the cord are undergoing degeneration. Certain it is that the saliva is really increased in these cases of bulbar paralysis, and that the condition is not merely a loss of normal saliva occasioned by a paralysis of the muscles of the mouth. Indeed, the salivation is frequently present even before the muscles have become markedly weakened.

An increased flow of saliva may be caused, finally, by reflexes from other parts of the body, as from an ulcer of the stomach, from the uterus during pregnancy, from the trigeminal nerve in cases of trifacial neuralgia, etc.

In all these conditions the saliva presents the characteristics of that obtained by stimulation of the chorda tympani; *i.e.*, it is increased in amount, but poor in solids.

An increased secretion of saliva is especially unpleasant when it drips from the mouth, as happens in cases of bulbar paralysis. Yet even when it is swallowed it may be disadvantageous, for the large quantity of alkaline, mucous fluid, rich in bacteria, is injurious to gastric digestion.

Composition and Reaction of the Saliva.—The saliva may contain abnormal constituents, such, for example, as the compounds of iodine, when the latter have been administered. Whether other substances pass into the saliva or not depends largely upon the amount present in the plasma. Urea is thus excreted only in those pathological conditions which increase

its concentration in the blood, as in severe nephritis. Other constituents of the blood, such as sugar, rarely pass into the salivary secretion. It is unnecessary to enumerate the various substances which sometimes appear in the saliva, for the subject has but little pathological significance.

The reaction of the saliva varies in the healthy individual during the process of digestion. In the fasting condition it is usually weakly acid, but after taking food it becomes alkaline. On the other hand, in diabetes, in fever, and in dyspeptic individuals, it is not infrequently constantly acid; in some instances owing to the presence of the products of bacterial decomposition. The pure parotid saliva is said to be acid in severe diabetes, but the cause of the acidity is not known, and some observers have even found it to be alkaline in severe forms of the disease.[a]

Swallowing.—The passage of food from the mouth into the œsophagus is accompanied by special dangers, for it must cross the respiratory tract in the pharynx. The trachea must be closed off below by the epiglottis, and the nasal passage above by the soft palate and the superior constrictors of the pharynx. This intricate mechanism is controlled by reflexes through the trigeminal and vagus nerves. The centripetal impulses arise from the mucous membrane of the throat, and the centre which presides over swallowing is situated in the medulla.

Disturbances of the act of swallowing may be caused by a diminished irritability either of the centre or of the sensory nerves. This is seen in certain intoxications, notably morphine, chloroform, chloral, diabetic coma, and uræmic coma, as well as in some diseases of the nerves. Disturbance of swallowing may also arise from a paralysis of the necessary muscles, caused either by a disease of the motor nuclei in the medulla, as in bulbar paralysis or medullary tumors, or by a neuritis

[a] Gamgee, Phys. Chem d. Verdauung, Leipzig, 1897, p. 50.

of the nerves themselves, such as is seen so frequently after diphtheria. Furthermore, difficulty in swallowing may arise not from a paralysis, but from a spasm of the necessary muscles, as occurs in hydrophobia, tetanus, and hysteria. Finally, defects in the palate, usually caused by syphilitic ulcerations, interfere with the act of swallowing.

In these conditions, the food may pass either into the nose or into the trachea. The latter is the more serious, for if the food, with its many bacteria, enters the lungs, pneumonia and not infrequently gangrene result. The entrance of food into the nasal cavity is less dangerous. Coughing and sneezing are the usual results. Yet these may cause the patient such great discomfort that he refrains from eating, and it is even possible that a large portion of his nourishment should be lost through the nose.

When swallowing is painful, the patient may take insufficient nourishment, just as is the case when chewing is painful.

Œsophageal Stenosis.—Diseases of the œsophagus usually produce symptoms by obstructing the passage of food. This obstruction may be due, in the first place, to a muscular spasm, as in hydrophobia and hysteria. Such an œsophageal spasm is rarely very serious, because in the case of hysteria it is usually finally overcome, and in hydrophobia there are other more immediate dangers.

Of greater importance are permanent obstructions, such as may be caused by the contraction of scar tissue, by tumors, or by pressure from without. The milder stenoses only interfere with the swallowing of the coarser foods; the more severe ones may stop even fluids. Normally we do not feel our food after it has once passed the pharynx, but the patient with an obstruction in his œsophagus often complains that he can feel the food stop in a definite place. Above the point of obstruction the œsophagus usually becomes dilated, owing to the stasis of material. The muscular tissue surrounding the dila-

tation undergoes hypertrophy, and it is then probably better able to force food past the stenosis. Some of that which does not pass stagnates *in situ*, undergoing decomposition. The remainder is immediately returned into the mouth. This regurgitation of food is quite different from vomiting, and the patient himself usually appreciates the difference; for the food swallowed appears to return of itself, he experiences no nausea, and his abdominal muscles are not brought into action. Apparently the obstruction to the passage of food increases the contractions of the muscular tissues of the œsophagus. Many believe that the increased pressure on the food simply forces it upward, and that there is no true antiperistalsis in these cases. Personally, however, I see no reason to exclude the possibility that antiperistaltic movements do play a part in the regurgitation of food.[5]

Pressure Diverticula.—The so-called pressure diverticula usually spring from the upper and posterior part of the œsophagus. They seem to originate from a primary weakness of the œsophageal wall, produced by such causes as foreign bodies, traumatisms, or possibly congenital defects in the muscle. The wall of the diverticulum is composed of the mucous membrane, the submucosa, and a thin layer of muscle. As the sac becomes larger, a part of the food passes into it instead of going down the œsophagus. This food is in part immediately regurgitated, but enough may remain in the diverticulum to press upon the œsophagus and so to occlude it. It is only after the sac has been emptied of its contents that a free passage is again opened into the stomach. The symptoms caused by such a diverticulum vary greatly, depending, for the most part, upon the ease with which the sac is filled and emptied. The food which stagnates in the sac may decompose and cause ulcerations of the mucous membrane, and these in turn may give rise to

[5] Starch, Arch. f. klin Med., vol lxvii. pp. 1, 201, 383; Brosch, ibid., vol. lxvii. p. 45; Riebold, ibid., vol. lxxx. p. 527

very severe pains. A pressure diverticulum is therefore a considerable menace to the health of the patient, and it is fortunate that the condition is a rare one.

Primary Dilatation of the Œsophagus.—Difficulties in swallowing may be caused by a diffuse or localized œsophageal dilatation, unaccompanied by any demonstrable anatomical obstruction.[6] It is very probable that in many of these cases the dilatation is due to a functional stenosis, originating in a spasm of the muscle at the lower end of the œsophagus. Such spasms may be primary, or they may be caused by ulcerations of the mucous membrane. In some instances the dilatation has a congenital origin. The symptoms of such dilatations are very similar to those of ordinary stenoses,—viz., obstruction to the passage of food, stasis in the dilated sac, and regurgitation. When there is a partial anatomical stenosis, or a functional stenosis from spasm of the cardia, the symptoms may persist for many years with intermissions of perfect health. The symptoms sometimes resemble those of rumination, especially if the dilatation affects that portion of the œsophagus which lies between the diaphragm and the cardiac orifice of the stomach.

In another class of cases, the course of the disease is exceedingly rapid, and autopsy discloses an œsophagus widely dilated, filled with food, and yet without any demonstrable stenosis. A condition similar to this may be produced experimentally by cutting both vagi in the neck of a dog.[7] This operation causes a paralysis of the œsophageal musculature, so that, even though the cardia apparently remains open, food does not pass into the stomach, but accumulates in the œsophagus and causes death. The cases of acute œsophageal dilatation in man, above referred to, are probably due to just such a primary paralysis of the muscle, depending possibly upon a lesion of the vagi nerves.

⁶ Zusch, Arch. f. klin. Med., vol. lxxiii. p. 208.
⁷ Krehl, Du Bois' Arch., 1892, p. 278.

Painful sensations rarely originate in the œsophagus, first, because painful affections, such as ulcer, are rare in this portion of the digestive tract, and secondly, because this is a comparatively insensitive organ. Yet, as we have already mentioned, diverticula may occasion great pain.

Rupture of the œsophagus is very rare. It is usually a complication of some definite lesion of the wall, such as carcinoma or erosion from acids or alkalies. It may, however, occur in apparently healthy individuals, though the cause of the rupture in such cases is unknown.

The Stomach.—The stomach acts as a reservoir for the large quantities of food which are ingested at each meal. Some of this food is absorbed in the stomach, but most of it, including practically all the water, is gradually passed on into the duodenum, after having been acted upon by the gastric juice. Strangely enough, the opinion has become current that the stomach is a superfluous organ. It is, indeed, true that animals as well as men have continued to live after the stomach has been practically entirely extirpated, and that life may be maintained by artificially introducing food into the intestines below the stomach.[8] Indeed, a dog without a stomach may live on quite a varied diet, even though it include decomposing meat.[9] Interesting and important as these facts are, nevertheless it remains true that the less a man has cause to consider his digestion, the better is his health; and the stomach stands as a most important preparatory organ, which receives the varying kinds and quantities of food, and shields the more delicate intestines from the harm which these foods might produce if directly introduced.

It is possible to obtain pure gastric juice from animals,[10]

[8] Kaiser, Czerny's Beiträge, 1878; Ogata, Du Bois' Arch., 1883, p. 39; Deganello, Arch. ital. de Biol., vol. xxxiii. p. 118.

[9] Carvallo and Pachon, Arch. de physiol., 1894, p. 106.

[10] Pawlow, The Work of the Digestive Glands.

but from man we are only able to obtain mixtures containing both gastric juice and food. For this reason it is impossible to make very accurate studies of the gastric secretion of man.

At the height of digestion the hydrochloric acid is present in the stomach in various combinations. In the first place, some has united with the inorganic bases or basic salts of the food, or has even decomposed salts of the weaker acids. Secondly, a portion of the hydrochloric acid combines with certain basic organic compounds.[11] Of these, the most important practically are the combinations between the hydrochloric acid and the various proteids of the gastric contents. These combinations possess an acid reaction and some antiseptic properties, and are able to assist the pepsin in hydrolyzing proteids, though their action here is less efficient than is that of free hydrochloric acid. Finally, a certain amount of free, uncombined hydrochloric acid is usually present in the gastric contents. Yet this may be absent, even at the height of digestion, in some individuals, and it is questionable whether such an absence is always pathological or not, for some of these individuals appear to be in perfect health.

The total amount of acid secreted depends mainly upon the quantity and quality of the food taken. The secretion apparently continues until the free and combined hydrochloric acid in the gastric contents reaches a certain percentage, amounting normally to about 0.2 to 0.3 per cent. Precisely to what degree the secretion of acid depends upon the quantity of nourishment, and to what degree it is subject to individual variations, has not been completely worked out. Organic acids may be introduced in the food, but they are not formed in the healthy stomach,[12] and lactic acid, for example, is never a product of normal gastric digestion.

[11] F. A. Hoffman, Ztrbl. f. in. Med., vol. xi. p. 521.

[12] Martius and Leuttke, Die Magensäure des Menschen, Stuttgart, 1892; Boas, Ztft. f. klin. Med., vol. xxv. p. 285.

The Disturbances of Gastric Secretion.—The mucous membrane of the stomach usually continues to manufacture the zymogens of pepsin and rennin, even though the secretion of hydrochloric acid has partly or wholly ceased. Only in the most advanced changes of the mucosa are these ferments much diminished or altogether absent. Such a lack of ferments may be seen in advanced atrophic gastritis, in carcinoma of the stomach, and in certain neuroses (so-called achylia gastrica). Thus no simple relation exists between the amounts of acid and of ferments present in the gastric juice.[13] The former is usually the first to disappear under pathological conditions, and the ferments may or may not follow it. The secretion of rennin and of the fat-splitting ferment [14] seems to vary simultaneously with the secretion of pepsin. In studying cases of impaired gastric secretion, therefore, it is necessary to consider both the acids and the ferments.

No symptoms are necessarily produced by a mere absence of gastric juice so long as the motility of the stomach remains good, and it is a remarkable fact that this motility is often increased in cases of achylia. We are still very poorly acquainted with the anatomical changes in the mucous membrane which lead to a cessation of gastric secretion, and especially are we ignorant as to the rôle which nervous influences may play in producing this condition.

What furnishes the normal stimulus to gastric secretion? In dogs, at least, the appetite plays a leading rôle,[15] but this appears to be less true for man. It would seem that the human mucous membrane is directly stimulated to secretion by the presence of proteid food in the stomach, and that this, together with certain reflexes, exercises a greater influence upon

[13] Roth, Ztft. f. klin. Med., vol. xxxix. p. 1; Gintl, Arch. f. Verdauungskr., vol. iv.; Troller, ibid., vol. v. p. 150.

[14] Volhardt, Ztft. f. klin. Med., vol. xlii. p. 414.

[15] Pawlow, The Work of the Digestive Glands; Lang, Arch. f. klin. Med., vol. lxxviii. p. 302.

gastric secretion than does the appetite.[16] The saliva and the chewing of food may also be of some importance.[17]

(Recent observations [18] upon a patient with a gastric fistula have furnished us with some important data concerning human gastric juice and the factors which influence its secretion. The stomach of this patient was found to be empty so long as he fasted, providing that he took care not to swallow his saliva. Chewing gum did not give rise to a gastric secretion, whereas the chewing of food or the mere rinsing out of the mouth with brandy was sufficient to start the flow of gastric juice, evidently because these articles stimulated the appetite. Even the mere passage of food before the eyes of the hungry patient was enough in one instance to excite a flow from the stomach. In view of these direct observations, which are completely analogous to those made by Pawlow on dogs, it cannot be doubted that the appetite plays a most important part in regulating the gastric secretions of man.

The secretion obtained in these experiments began about three minutes after the introduction of food into the mouth, and reached its maximum in from ten to fifteen minutes, finally ceasing after about an hour. The hydrochloric acid was present in greatest concentration during the first half-hour, and reached as high a percentage as 0.35 per cent.—Ed.)

Hypersecretion of Gastric Juice.—The stomach of a healthy fasting man is either empty or it contains a small amount of fluid, which may or may not show free acid. Some authors believe that the fasting stomach is always empty,[19] while others hold that it usually contains active gastric juice which sometimes amounts to fifty or one hundred cubic centimetres. In our experience it has been found empty in some

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[16] Schüle, Arch. f. klin. Med., vol. lxxi. p. 111.

[17] Schüle, Arch. f. Verdauungskr., vol. v. p. 165.

[18] Umber, Berl. klin. Wochens., 1905, p. 56.

[19] Reigel, Nothnagel System; Ewald, Klinik d. Verdauungskr.

cases, while in others it has contained a small quantity of secretion, possibly caused by material (saliva) swallowed.

Pathologically, the stomach may contain large amounts of fluid, even when the patient is fasting. The percentage of hydrochloric acid in this abnormal secretion may be normal or it may be excessive, up to 0.4 or 0.5 per cent. After a meal the secretion and the percentage of acid may be still further increased; yet this does not always occur, and it is possible that at the height of digestion the gastric contents of these patients should appear to be perfectly normal.

Such a continuous hypersecretion has been met with in chronic dyspepsia.[20] It may also occur as a transitory or periodic condition in certain nervous diseases,—such as tabes, neurasthenia, and hysteria.[21] The cause of the hypersecretion appears to be an increased irritability either of the mucous membrane of the stomach or of its secretory nerves. In many cases, even after a long period of hypersecretion, no anatomical changes are demonstrable in the gastric mucous membrane,[22] which would seem to indicate that, in these cases at least, the condition was of nervous origin. It is possible that a hypersecretion may sometimes be caused by a stimulation of the secretory centres in the brain, and, when this is so, the condition would be comparable to the salivation that is so often present in progressive bulbar paralysis.

Chronic hypersecretion is frequently met with in association with dilatation of the stomach. A number of clinicians, among them Riegel, regard the dilatation as secondary to the hypersecretion. According to others,[23] however, the dilatation is

[20] Reichmann, Berl. klin. Wochens., 1882, No. 40, 1884, No. 48, 1887, No. 12; Riegel, Deut. med. Wochens., 1904, Nos. 20 and 21.

[21] Ewald, Klinik d. Verdauungskr.; Rossbach, Arch. f. klin. Med., vol. xxxv. p. 383.

[22] Oestreich, Verein f. in. Med., in Berlin, Deut. med. Wochens., 1895, No. 21; Ferrand, Centralbl. f. Path., vol vii. p. 769.

[23] Schreiber, Arch. f. Verdauungskr., vol. ii p. 423.

primary and the hypersecretion results from an over-stimulation of the mucous membrane by the stagnated food.

In all these conditions the secretion of gastric juice is continuous even during fasting. In another group of cases, the stomach is found to be empty between meals, but when food is introduced it reacts with an over-production of normal gastric juice or with the production of an abnormally acid secretion. In this subject we are greatly handicapped by our relative ignorance as to the manner in which the stomach normally responds to the introduction of various kinds and quantities of food. It is usually assumed that the large amount of acid present in these cases is hydrochloric acid, and in most instances this is certainly true, for an acidity of 0.5 per cent. in the absence of organic acids allows of hardly any other interpretation. Still a greater precision in this matter is desirable.

Round Ulcer of the Stomach.—Round ulcer of the stomach is usually accompanied by hyperacidity. The relation between the two is of interest, because some authors have held that the excess of acid produces the ulcer. That some relation does exist between the two is shown by the fact that round ulcers only occur in localities exposed to acid secretions (stomach and duodenum). Yet, ordinarily, abrasions of the gastric mucous membrane heal with great rapidity.[24] The wall of the stomach contracts opposite the injured point, which is thus somewhat protected from the action of the gastric juice, and the epithelium then rapidly extends over the defect. The round ulcer of the stomach as seen in man differs from such an abrasion mainly in its chronicity.

A double etiological relation seems to exist between hyperacidity and ulcer of the stomach. .On the one hand, the irritation of the nerves at the base of the ulcer seems to increase the secretion of gastric juice. On the other, a hyperacidity

[24] Matthes, Ziegler's Beiträge, vol. xiii. p. 309; A. Schmidt, Kongr. f. in. Med., 1902, p. 270.

would interfere with the healing of any defect in the mucous membrane, and an anatomical lesion would then be more liable to lead to a chronic ulceration. A number of facts indicate that the hyperacidity alone is not the cause of the ulcer. Thus ulcers may occur without hyperacidity,[25] though it must be admitted that in these cases the latter may have been present at some earlier stage of the process. Conversely, individuals may show a most marked hyperacidity for years without developing an ulcer. Other factors must therefore be present, and at best the hyperacidity is only a contributing cause. Of other factors which have been described, we may name general anæmia, local anæmia of the gastric mucosa, produced by thrombosis of blood-vessels, etc., and, finally, local traumatisms, whether mechanical, thermic, or chemical. The acid does not apparently attack the healthy mucous membrane, yet it may possibly do so if the latter is weakened by some of these accessory causes When the ulcer has once formed, the acid seems to prevent the formation of healthy granulation tissue, the base of the ulcer becomes thickened, and healing is rendered difficult.[26]

(Infectious thromboses situated in the gastric mucous membrane seem to be capable of leading to acute ulcers, the so-called hemorrhage erosions. This is apparently the cause of the severe gastric hemorrhage which sometimes follows an abdominal operation. Chronic round ulcers, however, rarely follow these erosions.

Experimentally it is extremely difficult to produce a gastric ulcer that presents the anatomical features characteristic of the chronic round ulcer of man. As has been previously stated, a mere abrasion of the epithelium, from whatever cause, generally heals quite rapidly. The most successful experiments

[25] Gerhardt, Deut. med. Wochens., 1888, No 18; Lenhartz, ibid., 1890, No. 60; Du Mesnil, Münch. med. Wochens., 1894, No. 50.

[26] Korczynski and Jaworski, Arch. f. klin. Med, vol. xlvii. p. 578.

are those in which the pneumogastric nerves of rabbits have been divided.[27] Following this operation, round ulcers of chronic course and of typical anatomical structure have developed in some instances. It is not known in what way section of the vagi affects the gastric mucosa, whether it is by interfering with protective reflexes or by shutting off trophic influences. No observations, directed to the possibility that the round ulcer of man might be caused by lesions of the vagus nerve, have yet been made.—ED.)

Effects of Hypersecretion and Hyperacidity.—In discussing the effects of an excessive secretion of hydrochloric acid, it is possible to consider both hyperacidity and hypersecretion together. Disturbances are produced by the excess of acid; and these occur during digestion in cases of pure hyperacidity, or during fasting in cases of continuous hypersecretion. As Riegel has said, the effects result in both cases rather from the profuse secretion than from the high acidity of the juice secreted. In the presence of an excess of acid, the digestion of starch in the stomach ceases altogether. The proteids are digested, but it is not known whether this digestion follows a normal course or not. The patient frequently suffers from severe pains and from vomiting, for both of which the hyperacidity is usually directly responsible, for they are usually relieved by the administration of substances which will combine with acids, such as alkalies and proteids.

The effect of an increased secretion upon the gastric motility will be discussed in another place, though we may mention here that not infrequently a hypersecretion is followed by dilatation of the stomach (Riegel). What effect the hyperacid gastric contents exert upon the intestines and upon the intestinal digestion is not definitely known. Possibly the poor nutrition of many patients with hyperacidity is due to the

[27] van Yzeren, Ztft. f. klin. Med., vol. xl. p. 181; W. Ophüls, Personal Communication.

difficulty in neutralizing the hyperacid material which reaches the intestines and to a consequent insufficient absorption of nourishment.

The symptoms of gastric ulcer are, in part, those of hyperacidity; yet the pains are usually more intense, probably because the base of the ulcer is especially sensitive. Then, too, a series of complications may follow in the train of the ulcer. Arteries may be eroded and hemorrhage ensue; the gastric wall may be perforated, with the resultant adhesions, abscesses, or peritonitis. The number of such complications is unfortunately a large one.

Subacidity and Anacidity.—It is necessary to be very careful in our judgment of those cases in which the amount of free hydrochloric acid in the gastric contents is found to be diminished, for this may be brought about in two ways,— either by an actual diminution in the secretion, or by a neutralization in some abnormal manner of the acid secreted. To estimate the total amount of hydrochloric acid secreted it is necessary to know the total quantity of chlorides in the gastric contents, and to subtract from this the chlorides of the food.

Free hydrochloric acid is absent in many acute gastric disturbances, functional as well as anatomical, notably in those associated with the acute infectious diseases. Anacidity is seen more frequently, however, in chronic diseases of the stomach, as in atrophy or amyloid degeneration of the mucous membrane, and especially in carcinoma. Even diseases outside of the stomach may inhibit the gastric secretion; and carcinomata situated in the abdominal cavity, pernicious anæmia, advanced tuberculosis, and cachexia may all be associated with an absence of free hydrochloric acid in the gastric contents. A mere reduction in the amount of the free hydrochloric acid occurs in a great variety of conditions, especially in the chronic dyspepsias. In all these cases more data are needed as to the total amount of acid which has been secreted.

These relations have been carefully studied in gastric carcinoma. The diminution or absence of free hydrochloric acid in the stomach contents of such patients may be due, as we have said, either to a lessened secretion of acid or to an increased production of compounds which will bind the acid. Both conditions appear to be present in cases of gastric carcinoma. The diseased condition of the gastric mucous membrane which is demonstrable in many cases of carcinoma might readily lead to a diminished secretion of acid.[28] On the other hand, the carcinoma apparently produces substances which tend to neutralize the acid secreted, and in many cases considerable hydrochloric acid must be added to the gastric contents before a reaction for free acid will appear. The substances which cause the acid to disappear are apparently of the nature of enzymes, for they are destroyed by heat.[29] That hydrochloric acid is secreted in carcinoma is shown by the fact that the quantity of combined chlorides may equal or exceed the normal.[30] If the carcinoma develops on an old ulcer of the stomach, free hydrochloric acid is usually present in the gastric contents, and often in excessive quantities.[31]

When the hydrochloric acid in the gastric contents is reduced, the ptyalin is able to act for a long time upon the food, unless its action should be interfered with by the presence of organic acids. Digestion of the proteids is usually diminished or absent, according to the reduction in the amount of hydrochloric acid. (A carcinoma of the stomach, however, apparently produces ferments which are able to decompose proteids even more rapidly than does the normal gastric juice.[32]—Ed.)

[28] Rosenheim, Berl. klin. Wochens., 1888, Nos. 51 and 52; Hammerschlag, Arch. f. Verdauungskr., vol. ii. pp. 1, 198; Reissner, Ztft. f. klin. Med., vol. xliv. p. 87.

[29] Emerson, Arch. f. klin. Med., vol. lxxii. p. 415.

[30] Cahn and Mering, Arch. f. klin. Med., vol. xxxix. p. 233; Reissner, Ztft. f. klin. Med., vol. xliv. p. 87.

[31] See Hirschfeld, Kongr. f. in. Med., 1902, p. 279.

[32] See Emerson, loc. cit.

A diminished proteid digestion in the stomach does not necessarily mean a loss of food material to the body, for with a proper dietary the intestinal digestion can compensate for the inefficiency of the stomach, and the nitrogenous material in the body may not only be maintained at the old level, but in some cases the store may be actually increased.[33]

Bacterial Action in the Stomach. An abundant multiplication of bacteria within the stomach is prevented mainly by the normal evacuation of its contents. Even though hydrochloric acid is absent, no bacterial decomposition ordinarily takes place so long as the motility of the stomach remains good and its contents are regularly passed on into the intestines before the bacteria have time to multiply. The main factor favoring bacterial decomposition is stagnation of material, and, when this is present, the grade of acidity present plays a most important part in determining the variety of micro organisms which shall multiply, and consequently the character of the decompositions which these shall produce.

The normal gastric juice possesses decided antiseptic properties, owing principally to its acidity. Whether the pepsin is of great importance or not in this respect is still a matter of dispute. Cells are usually digestible only when they are dead; yet it has been claimed that the pepsin plays an important part in limiting bacterial growth, more especially the growth of those bacteria which give rise to the lactic acid fermentation.[34] An acidity of 0.2 per cent. in a test-tube will after a time destroy many bacteria, such, for example, as the typhoid bacillus and the cholera vibrio, whereas other bacteria and especially spores are not greatly injured by this amount of acid. Yet the conditions in the test-tube are not the same as those in the stomach Many parts of the food do not come into intimate contact with the gastric juice at all, either because they

[33] v. Noorden, Ztft. f. klin Med. vol. xvii. pp. 137, 452, 514.

[34] Hammerschlag, Arch. f. Verdauungskr., vol ii. p. 1.

are quickly passed on into the intestines or because they lie in the centres of large particles which are not broken up in the stomach. Furthermore, a large part of the hydrochloric acid secreted is immediately bound by the proteids, etc., and these combinations are known to be less antiseptic than is free hydrochloric acid, though even they may kill cholera bacilli.[35] It is evident, therefore, that the bactericidal powers of the gastric secretion are limited, and that numbers of micro-organisms are being constantly passed on into the intestines.

If free and abundant hydrochloric acid be present in stagnated gastric contents, the ordinary putrefactive decompositions of proteid material rarely take place. The fermentation of carbohydrates, however, does occur: sugar is transformed into alcohol and carbon dioxide, alcohol into acetic acid, dextrose into lactic acid, butyric acid, carbon dioxide, and hydrogen, etc. The gases which ordinarily result from these fermentations are carbon dioxide, hydrogen, and traces of methane. These, together with swallowed air, usually make up the bulk of the gases present in the stomach during gastric fermentations.[36] Each of these fermentations may be carried on by a number of micro-organisms that will resist an acid reaction of not too high a grade,[37] but yeasts and sarcinæ are those most commonly found.

If the stagnation is accompanied by a diminution or absence of hydrochloric acid, then opportunity is given for the multiplication of a greater variety of micro-organisms. These may even cause putrefaction of proteid material. More frequently, however, they give rise to fermentative processes similar to those just described. Yet there is a special tendency to the

[35] Minkowski, Mitth. aus d. med. Klinik z. Königsberg, Leipzig, 1888; Kabrehl, Arch. f. Hyg., vol. x. p. 382.

[36] Hoppe-Seyler, Kongr. f. in Med., 1892, p. 392; ibid., Arch. f. klin. Med., vol. l. p. 82.

[37] Strauss and Bialoour, Ztft. f. klin. Med., vol. xxviii. p. 567.

production of lactic, butyric, and other volatile organic acids.[38] The lactic acid fermentation is particularly characteristic of gastric stagnation in the absence of hydrochloric acid; and if this be present in sufficiently large quantities it tends to inhibit the growth of many bacteria which would otherwise give rise to putrefactive processes. A special lactic acid bacillus (Oppler-Boas bacillus) is then frequently present in enormous numbers in the gastric contents.

From a consideration of these facts it will be seen that no one kind of bacterial decomposition is pathognomonic of any particular clinical condition. The decomposition depends rather upon the varieties of micro-organisms which have been introduced into the stomach, upon the opportunity which they have had to multiply, and upon the kind of food which is subjected to their activities. The relation between carcinoma of the stomach and the lactic acid fermentation must be judged from just such a general stand point. The two frequently occur together; but this depends upon the fact that stagnation, absence of free hydrochloric acid, and diminution in the ferments are frequently present in carcinoma of the stomach, and that these are the very conditions which favor the development of the lactic acid fermentation. If, as rarely happens, the combination of a gastric stagnation and an absence of free hydrochloric acid is caused by some condition other than carcinoma, then the lactic acid fermentation might equally well occur there. Very remarkable decompositions have been observed in some stomachs, such, for example, as the production of sulphuretted hydrogen when free hydrochloric acid was absent.[39]

The acidity of the gastric contents exerts no small influence upon the chemical processes in the intestines, and we may say here that, in general, as the acidity in the stomach dimin-

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[38] Rosenheim and Richter, Ztft. f. klin. Med., vol. xxviii. p. 505

[39] Boas, Deut. med Wochenschr., 1892, No. 49.

ishes, the putrefaction in the intestines tends to increase. This subject will be more fully considered below.

It sometimes happens that fermentation occurs in the gastric contents, even though there is no diminution either in the secretion of acid or in the motility of the stomach. In such cases it is possible that the fermentation is due to the introduction of excessive amounts of fermentable material, together with the agents which cause the fermentation.[40] This fermentation would in turn affect the gastric motility, and that would favor further fermentation.

Abnormal fermentative processes do harm to the stomach in various ways. The products of fermentation may irritate and injure the gastric mucosa, producing loss of appetite, pains, vomiting, and possibly spasmodic stricture of the pylorus with diminished gastric motility. Gases may be produced in large quantities, causing abdominal distention and belching. The abnormal secretion of fluid by the stomach, together with the distention by gases, would favor the development of gastric dilatation. At times toxic substances are produced in gastric fermentations, and these may give rise to a varied category of general symptoms (see p. 259).

We know very little about the function of the mucus secreted by the stomach, which is unfortunate, because it is quite probable that this may exert some protective influence in certain pathological conditions.

THE DISTURBANCES OF GASTRIC MOTILITY

The normal movements of the different parts of the stomach are fairly well known. The fundus acts as a reservoir for the food. Its wall shows peristaltic movements, but the pressure within it is comparatively low. The antrum pyloricum contracts periodically, several times a minute, although it may at times contract irregularly. During a contraction the

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[*] Naunyn, Arch. f. klin. Med., vol. xxxi. p. 225.

pressure exerted upon its contents is considerable, over a half-
metre of water in man.[41]   Since its cavity is shut off from the
fundus by the sphincter-like action of its proximal portion, its
contents may be thrown through the relaxed pylorus into the
intestines.   (The relaxation of the pylorus in the normal stom-
ach seems to depend upon the presence of free hydrochloric
acid in the stomach contents.   When particles of food are
present in the stomach, the pylorus is closed, but with the
appearance of free acid it relaxes, and some of the acid con-
tents are allowed to pass through into the intestines.   The
effect of the acid within the duodenum is to cause, on the one
hand, a closure of the pylorus behind, and, on the other, to
stimulate the flow of the alkaline secretions of the pancreas.
These will in time neutralize the acid in the duodenum, and
when this is effected the pylorus can again relax and allow
more of the acid gastric contents to pass through.   By this
mechanism a gradual emptying of the stomach into the intes-
tines is affected.   Since proteids combine with the acid which
is first secreted, and thus delay the appearance of free acid in
the gastric contents, they do not leave the stomach so soon
as do carbohydrates or fats.[42]—ED.)   The antrum pyloricum
seems to pick the fluid and finely divided portion of the gastric
contents out of the fundus, and in this manner it regulates still
further the emptying of the stomach.[43]

The cause of the gastric movements is very uncertain.   In
the first place, like all other unstriated muscles, the stomach
has periods of rest alternating with periods of activity.   Some
have believed that the acidity exerts a great influence upon the
gastric movements, yet we know that, under pathological con-
ditions at least, no definite relation exists between the motility
of the stomach and the acidity of its contents.   On the one

[41] Mortiz, Ztft. f. Biol., vol. xxxii. p. 313.
[42] Cannon, Jour. of the Am. Med. Assoc., 1905, p. 15.
[43] v. Mering, Kongr. f. in Med., 1897, p. 433.

hand, we see diminished motility combined with hyperacidity, and, on the other, increased motility with an entire absence of free hydrochloric acid. The consistency of the contents certainly influences gastric motility. Large solid particles are thrust back into the fundus by the antrum, whereas soft masses are allowed to pass through into the intestines. Warm material tends to increase the peristalsis and to relax the pyloric sphincter.[44] Although careful studies have been made as to the length of time that certain foods remain in the stomach, yet more work is needed upon abundant mixed diets.[45]

Increased Peristalsis and Increased Gastric Motility.—At times, the peristaltic movements of the stomach are increased, and its contents are emptied more rapidly than normal. Yet this rapid emptying does not necessarily occur; for, when a hinderance to the exit of food is present, the powerful contractions of the muscle may be unable to expel the food even within the normal period of time. Frequently the patient is rendered extremely uncomfortable by the excessive gastric peristalsis, and the movements of the stomach may be plainly visible through the abdominal wall. In some cases this condition of "peristaltic unrest" is dependent upon a primary pyloric stenosis; in others, it is probably caused by an excessive irritability of the nervous connections of the stomach, and it is then frequently accompanied by violent peristalsis of the intestines. As we have already said, the stomach may empty itself with unusual rapidity in achylia gastrica, though this rapid emptying is not usually associated with any sensations of increased peristalsis.

Motor Insufficiency and Gastric Dilatation.—Whenever the stomach does not empty itself within the normal limits of time, we speak of a motor insufficiency. So long as the disturbance of motility is slight, it may be of but little conse-

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[44] Schüle, Ztft. f. klin. Med., vol. xxix. p. 80.
[45] Penzoldt, Arch. klin. Med., vol. li. p. 535.

quence; but should it become so pronounced that food particles remain continuously in the stomach, then fermentations are apt to injure the mucous membrane owing to the production of abnormal acids and to distend the muscle by abnormal gases, and then a dilatation of the stomach may ensue. This dilatation is especially favored in some instances by the secretion of large quantities of fluid, for these are not readily absorbed by the stomach, and they throw additional work upon an organ which already empties itself poorly.[46] That the stagnation of food in the stomach directly influences the gastric secretion has been proved by the changes in the secretion [47] which follow drainage of a stomach after a successful gastroenterostomy.

(Dilatation is therefore one of the most striking, and at the same time one of the most serious results of a motor insufficiency. Yet the two do not necessarily run a parallel course. On the one hand, the gastric motility may be impaired without any dilatation, while on the other it is possible to have an enlarged stomach without motor insufficiency. In the former case the stomach empties itself slowly and may even never become completely emptied; yet it does not become distended, for the reason that there is an absence of the other factors necessary to produce this result, such as the accumulation of abnormal amounts of gases, fluids, etc. In the latter case the muscular tonus of the stomach is lessened, and the organ dilates; yet at the same time it empties itself of food within the normal limits of time.

If large quantities of food or drink are habitually taken, the cavity of the stomach becomes enlarged, as has been repeatedly observed in Munich beer-drinkers. This dilatation is necessary and of a compensatory nature, and it is usually not

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[46] v. Mering, Kongr. f. in. Med., 1893, p. 471; Miller, Arch. f. Verdauungskr., vol. i. p. 233.

[47] Kausch, Mitth. aus d. Grenzgeb., vol. iv. p. 347.

associated with any motor insufficiency. It may well be compared to the dilatation of the left ventricle that regularly accompanies a compensated aortic insufficiency (see p. 34). A dilatation of this character has an entirely different significance from that caused by a relative weakness of the gastric musculature. Clinically it is customary to designate the difference between the two by calling the former a large stomach (megalogastria) and the latter a true dilatation.—ED.)

Causes of Dilatation.—Dilatation may result from a variety of causes. In the first place, it may follow a mechanical stenosis of the pylorus, such as may be caused by tumors, contracted scars, or pressure from without. It is quite probable also that it may follow a spastic contraction of the pyloric muscle, which arises from reflexes from ulcers, from sensitive spots on the mucosa, or perhaps from the irritation of a normal mucous membrane by caustic substances or even by hyperacid secretions.[48]

Every stenosis of the pylorus increases the work of the muscle in the antrum pyloricum. This additional work causes the muscle to hypertrophy just as additional work elsewhere will lead to an hypertrophy of the corresponding muscle. The more powerful contractions of the hypertrophied gastric muscle may for a time neutralize the effects of even a considerable stenosis. To what extent this is possible depends upon the relation existing between the degree of stenosis and the strength of the hypertrophied muscle. Ultimately the hinderance to the exit of food may exceed the compensatory power of the antrum, and then the stomach will no longer be able to empty itself completely. Dilatation then begins, and this dilatation is frequently favored by a concomitant weakening of the antrum caused by a degeneration of its smooth muscle-fibres.

Anomalies in the form and position of the stomach may also lead to dilatation. Changes in its immediate surroundings,

[48] Rüdimeyer, Arch. f. Verdauungskr., vol. vii.

tight lacing, enteroptosis,—all these exercise a most pronounced influence upon the ability of the stomach to empty itself. Such conditions may cause, in the first place, an actual narrowing of the gastric outlet, as happens, for example, when an abnormally low stomach presses upon or kinks the duodenum. Then, too, the low position of the fundus in gastroptosis increases the difference in the level between it and the pylorus, and renders a greater amount of work necessary to lift the contents out of the stomach. Remarkable acute dilatations [49] sometimes follow laparotomy, the stomach becoming enormously distended within a few hours. In some of these cases the dilatation apparently results from an acute obstruction which is caused by a kinking of the duodenum.

In other cases of gastric dilatation no hinderance to the exit of food is apparent. Such dilatations have been met with in chronic gastritis, ulcer, and carcinoma, in cases of hyperacidity and hypersecretion, and finally in association with enteroptosis, neurasthenia, and diseases of the spinal cord.[50] Some of these should perhaps be classified with those in which a functional stenosis exists, for it seems probable that a dilatation may follow a spasm of the pylorus, such as may accompany gastric ulcer or marked hyperacidity. In other patients mechanical factors of various kinds, such as an abnormally low fundus, may have interfered with the motility of the stomach. Yet, even after excluding all these, there still remains a group of cases for which no mechanical cause can be found and in which the dilatation is apparently caused by a primary weakness of the gastric musculature. Such have been termed atonic dilatations.

By atony is meant a lack of muscular tone. The atonic stomach is flaccid and contracts less firmly upon its contents

[49] Fleiner, Verdauungskr., vol. i. p. 352; Albrecht, Virch. Arch., vol. clvi. p. 285.

[50] Kausch, Mitth. a. d. Grenzgeb., vol. vii.

than does the normal organ. Consequently its cavity tends to become distended. The motility of such a stomach may be little or not at all impaired, in which case it empties itself within the normal period of time. More frequently, however, a motor insufficiency is present, and the food remains in the stomach longer than it should. (As a rule, this motor insufficiency is of the milder type, and the stomach does ultimately empty itself without allowing a continuous stagnation of its contents.—ED.)

Finally, gastric fermentation may cause a dilatation of the stomach.[51] Fermentation is, of course, a common sequel to dilatation, yet in some instances it is primary. In Naunyn's cases, dilatation and disturbances of gastric motility resulted from the introduction of large numbers of micro-organisms, together with easily decomposable food, and the dilatation disappeared as soon as the gastric contents were removed. The abnormal fermentation gave rise to large amounts of gas, which would undoubtedly interfere with the movements of the stomach. Possibly, also, the acid products of fermentation led to a reflex spasm of the pylorus.

Effects of Motor Insufficiency.—The results of a motor insufficiency of the stomach may be very serious. In the first place, if the obstruction at the pylorus is nearly complete, the patient will die from lack of nourishment, unless a communication be established by operative means between the stomach and the intestines. If the obstruction is incomplete, but yet sufficient to cause considerable stagnation, then favorable conditions are present for the growth of micro-organisms, and various abnormal decompositions will ensue. The presence or absence of free hydrochloric acid in the stagnated contents is an important factor in determining which micro-organisms can develop and what shall be the character of the abnormal decompositions. As a rule, an atonic stomach absorbs material

[51] Naunyn, Arch. f. klin. Med., vol. xxxi. p. 225.

poorly, and the retention of digestive products (albumoses, etc.) in the gastric contents will interfere to a certain extent with the further progress of digestion.[52] Possibly, also, abnormal quantities of true peptones are formed when the food remains in the stomach, and these cause a direct irritation of the gastric mucous membrane. Lastly, decomposed material and large numbers of bacteria are passed on into the intestines, where they may irritate the more delicate membrane and initiate further abnormal decompositions.

Very remarkable nervous symptoms sometimes develop as a result of gastric dilatation.[53] Of these we may name the fully developed and rudimentary forms of tetany, epileptiform convulsions, tonic muscular contractions resembling tetanus, and, finally, symptoms of general depression and collapse. These symptoms usually occur in cases in which dilatation is associated with hyperacid secretion, but the latter is not absolutely necessary. The cause or causes of these nervous symptoms are not well understood. One is tempted to assume that toxic substances are formed in the abnormal fermentations, and that these produce the symptoms by their action upon the nervous system. Indeed, French observers have prepared extracts from the stomach contents, and have shown that these may give rise to somewhat similar nervous disturbances.[54] Yet these experiments need careful confirmation before much weight is to be laid upon them. In some patients, no such poisons could be found, and Fleiner is of the opinion that mechanical causes, such as an overfilling of the stomach with a stretching of its parts, may play a more important rôle in the production of these symptoms.

[52] Chittenden and Amerman, Jour. of Phys., vol. xiv. p. 483

[53] Kussmaul, Arch. f. klin. Med., vol. vi. p. 471; F. Müller, Charité-Annalen, vol. xiii., 1888, p. 273; ibid., Kongr. f. in Med., 1898, p. 167; Ferranini, Ztrbl. f. in. Med., 1901, p. 1; Fleiner, Arch. f. Verdauungskr., vol. i. p. 243.

[54] Bouveret and Devic, Revue de médecine, vol. xii. p. 48.

Belching and Vomiting.—In addition to the normal movements of the stomach, others may occur which tend to empty its contents in the direction of the œsophagus. Waves of anti-peristalsis have been directly observed in cases of gastric dilatation.[55]

By belching, we understand an expulsion of gas from the digestive tract through the mouth. Air in the œsophagus is easily expelled, for a powerful inspiratory movement with a closed epiglottis will draw air into the œsophagus which may afterwards be expelled during expiration. The gases may, however, come from the stomach, and they then consist either of air which has been swallowed,[56] or of gases which have arisen from abnormal fermentations,—viz., carbon dioxide, hydrogen, and methane. The gas frequently carries with it small amounts of liquid into the throat, and if this contains fatty acids, as it frequently does in gastric fermentation, it gives rise to the burning sensations known as pyrosis. Hydrochloric acid itself may also be carried up, and it will also produce unpleasant acid sensations.

The combination of movements by which the gas is expelled consists, on the one hand, of a relaxation of the sphincter at the cardiac end of the stomach, and, on the other, of a contraction of the abdominal muscles and diaphragm, whereby the intra-abdominal pressure is increased. Possibly, in some cases, the stomach also assists by contracting upon its contents. This complicated mechanism is most frequently set in motion by reflexes from the stomach or peritoneum.

In certain cases, the same movements take the form of clonic spasm, and this produces the condition known as hiccoughing. Hiccoughing is also incited by reflexes from the stomach and peritoneum, but it may furthermore arise from

[55] Cahn, Arch. f. klin. Med., vol. xxxv. p. 402; Rautenberg, Arch. f. klin. Med., vol. lxvii. p. 308.
[56] Mathieu, Arch. f. Verdauungskr., vol. x. p. 29.

causes situated in the central nervous system, as is the case in the hiccoughing of hysteria, etc.

Vomiting is produced by a series of movements of the respiratory, abdominal, and gastric muscles, which follow each other in a certain sequence, and which finally culminate in the expulsion of the contents of the stomach through the mouth. Vomiting is initiated by a deep inspiration, which is then followed by a spasmodic contraction of the abdominal expiratory muscles, during which the glottis is closed and the diaphragm is held in a low position. The pyloric orifice is tightly contracted, the cardia is relaxed, and the stomach itself, though usually relaxed, may possibly perform anti-peristaltic movements. During the primary deep inspiration some of the gastric contents are probably aspirated into the œsophagus, for the circular muscles of this tube are relaxed and its longitudinal muscles are contracted. When, finally, the abdominal muscles contract, the intra-abdominal pressure is raised very greatly, and the contents of the stomach and of the œsophagus are expelled through the mouth.

This complicated mechanism is governed by a special centre in the medulla, situated not far from the respiratory centre. This "vomiting centre" may be acted upon directly by intra-cranial diseases and by poisons, or it may be stimulated re-flexly through the vagus fibres from the stomach, especially from the terminations of those which supply the neighborhood of the cardiac orifice. Vomiting may also be caused by reflexes from other organs, especially from the peritoneum, uterus, etc.

The act of vomiting not only affects the stomach but it also influences to a marked degree the general blood-pressure and the intrathoracic pressure. Traube has shown that at the beginning of the act the blood-pressure falls, and that the slow pulse is due to a vagus stimulation. Toward the end of the act both the blood-pressure and the pulse-rate are greatly

increased. The salivation and the sweating which occur at the beginning of vomiting demonstrate how wide-spread are the changes incident to this act.

Sensations arising from the Stomach.—A healthy man is not conscious of his stomach except when he is hungry or when the organ is overfilled. The sensation of hunger is undoubtedly dependent to a great extent upon the condition of the stomach, though we do not know the exact changes which give rise to this sensation. It seems probable that the intestines also influence the sense of hunger, for patients with intestinal fistulæ have been observed whose hunger was not fully satisfied when food was put into the stomach, but was satisfied if food material was also introduced into the intestines.[57] The mental condition likewise influences the sensation of hunger, as is well known. To what extent the needs of the body for new material influences the sensation is still uncertain; yet these needs do seem to exert some influence, and the hunger of diabetes as well as that following muscular exertion seem to be examples of " tissue hunger." Of all these various factors that may influence hunger the condition of the stomach is the most important.

Abnormally increased hunger is sometimes seen in patients with gastric ulcer or in those with hyperacidity, especially when there is an accompanying hypermotility of the stomach.

As a rule, however, gastric disturbances diminish the sensation of hunger, and the patient then has less inclination to take food (loss of appetite). Diminished hunger and loss of appetite are not precisely synonymous, for a person may say that he is hungry, and yet he will not eat, because he " has no appetite" for the food set before him. Loss of appetite accompanies many disturbances both of the gastric secretion and of gastric motility, but its exact cause is not known.

[57] Busch, Virch. Arch., vol. xiv. p. 140.

The sensations of fulness and pressure, which the healthy person experiences only after a full meal, become pathological if they are present when the stomach is not much distended. These sensations are produced more readily when the distention takes place rapidly than when it occurs gradually. This would seem to indicate that an increased tension of the stomach wall is an important factor in their production.

Gastric pain is frequently due to ulcerations of the wall of the stomach, whether these be round ulcers or are produced by carcinomata or by the action of corrosive poisons. It seems very probable that the pain in such cases is caused by the irritating action of the acid gastric contents upon the exposed base of the ulcer. Indeed, we know the acid may cause most intense pain, even when there is no ulceration. In such cases the pain may possibly result from a direct irritation of the terminals of the sensory nerves in the stomach wall; yet it seems more probable that, in most cases, it is due to a muscular spasm, more especially of the pyloric or the cardiac orifices. The sensations popularly known as cramps in the stomach may, therefore, in some instances, be actually due to spasms of the gastric musculature. As we have said, such cramps are frequently caused by hyperacid secretions or by ulcerations. Gastric pains may, however, be of a neuralgic character, and we are as ignorant concerning the nature of these as we are concerning the nature of neuralgias in general. The terrible pains which accompany the gastric crises of tabes and of other spinal affections are perhaps due to irritative degenerative processes in the pneumogastric nerve.

Disturbances of the stomach may lead to a great variety of symptoms in other parts of the body. We have already mentioned the attacks of tetany and related symptoms. There may also be various vasomotor disturbances, parasthesias, neuralgias, migraine, vertigo, as well as disturbances in the innervation of the heart (irregular action) and of the lungs

(cough). Some of these symptoms are of a reflex nature, others are probably due to poisons absorbed from the stomach. The investigation of this latter class of cases promises interesting results in the future.

It is especially characteristic of the stomach that disturbances of its function are combined in the most varied manner, and that one disturbance tends to bring others in its train. In certain cases it is possible to determine which of these is primary and which are secondary. In other cases we cannot make such a separation.

Functional disturbances of the stomach are not accompanied by constant anatomical changes, and the condition known as gastric catarrh is especially destitute of any well-defined pathological-anatomical basis. The relation between functional and anatomical changes in the stomach is not easily studied, because so few gastric disorders are fatal and because the stomach changes so rapidly after death. · For these reasons we know comparatively little about the relation between functional and anatomical changes in the stomach.

Not frequently patients complain of loss of appetite, nausea, and sensations of pressure in the abdomen, and yet the most careful investigation fails to reveal any secretory or motor changes. In a certain proportion of these cases it is possible that an unusual sensitiveness of the stomach exists, and that if the patients are careful in their diet they are relieved of the discomfort. In other cases, however, the symptoms seem to occur quite independently of the quantity and quality of the nourishment, and depend rather upon the psychic state of the individual. To this class of cases Leube has given the name of nervous dyspepsias. The frequency of nervous dyspepsia increases as the resistance of people to the unpleasant things of life diminishes. We all know the great influence our minds exert upon our digestion, and it is easy to conceive that this

influence might be pathologically intensified in neurotic individuals. Indeed, secretory and possibly even motor functions of the stomach may be thus influenced. Strümpell has termed such cases psychic dyspepsias.[58]

DISTURBANCES IN THE SECRETION OF BILE.

We know little of the variations which diseases cause in the amount and composition of the bile. Physiological experiments would seem to indicate that the amount is diminished in all those conditions in which but little food is taken. This diminution affects especially the water and the bile salts; but we are less certain as to the effect of inanition upon the bile pigments, for considerable variations in these occur normally.

Substances, not ordinarily present, may appear in the bile. Thus when the sugar in the blood exceeds 0.3 per cent., it is excreted by the liver, and the same is true of other substances, although this is apparently of but little practical significance. Albumin is said to appear in the bile in certain diseases. In certain others, especially in degenerations of the hepatic cells, and in the infectious diseases, the secretion of pigments is diminished, yet this occurs only in a minority of the cases. Further observations in this field are necessary.

It is possible to affect the composition of the bile through changes in the blood. When large numbers of red blood-corpuscles are destroyed, the liberated pigment is taken up by the various organs, especially by the liver (p. 141). This directly influences the bile. Its quantity at first is diminished, the formation of the pigments from the hæmoglobin is increased, and the bile salts are either normal or are diminished. Not infrequently the oxyhæmoglobin itself passes into the bile,[59] even long before it appears in the urine.

[58] Arch. f. klin. Med., vol. lxxiii. p. 672.
[59] Filehne, Virch. Arch., vol. cxxi. p. 605; Stern, ibid., vol. cxxiii. p. 33.

Certain poisons affect the composition of the bile. Of these, we may name toluylendiamin, arsenuretted hydrogen, and phosphorus. The first two destroy the red corpuscles of the blood, but phosphorus does not do so in mammals. In the earlier stages of intoxications with these compounds, the total quantity of the bile is usually diminished, the pigments are increased, and the bile salts only slightly increased or possibly diminished. Owing to an increase in its content of nucleoproteids, the bile becomes thick and viscid. In the later stages of these intoxications, the bile increases in quantity, its composition varying in different ways. These quantitative and qualitative changes are produced in part by the destructive action of certain of these poisons upon the red blood-corpuscles. Yet this is not the only cause of the biliary changes. The main factor seems rather to be a stimulation of the liver cells to the production of an abnormal secretion.

Gall-Stones.—Gall-stones usually originate in the gall-bladder. At times only one stone is found; more frequently, however, several or many are present. The numerous calculi so frequently found in the gall-bladder at autopsy are, in many instances, all of about the same size. In other instances they occur in groups, as, for example, one or two large, ten or twelve medium-sized, and fifty or more tiny stones. Such have been termed generations of gall-stones. The explanation for this grouping of stones seems to be that during some pathological process in the past several nuclei had originated, and that when once started the stones tended to act as centres about which the bile constituents should deposit. This continued until some change in the conditions in the bladder allowed a fresh set of stones to start.

Gall-stones are composed, for the most part, of cholesterin and of the calcium salt of bilirubin. Both these substances usually enter into the composition of the stone, but some

stones are composed entirely of one or the other of them. Other materials which may be present in biliary calculi are calcium carbonate, salts of the heavy metals, pure bile pigments, and derivatives of these pigments.

The precipitation of these substances out of the bile is not caused by their being produced in the body in abnormally large quantities. We know from Naunyn's observations that the amounts of cholesterin and of lime salts in the bile is in no way dependent upon the character of the food taken or upon the general metabolism. Cholesterin is held in solution in the bile by the cholates, soaps, and fats. This solution is not a saturated one, and cholesterin is not precipitated either by evaporating the bile or by allowing it to decompose. Undissolved cholesterin may be present in the bile, either because it has separated out of solution for the reason that the crystallization point has been reached, or because it has been carried into the bile undissolved by desquamated epithelial cells. The calcium salt of bilirubin seems to precipitate out of the bile only at a certain reaction and in the presence of proteids.

The most important causes which contribute to the precipitation of these substances from the bile are stagnation and infection. In old age the muscular tissue about the bile passages atrophies, and the normal movements of the bile are therefore interfered with. In women, lacing and pregnancy tend to distort the biliary tract and also to produce stagnation by pressure. Heredity seems to play some part in predisposing to the formation of gall-stones.

Stasis greatly favors the development of an infection of the biliary passages. The normal bile is usually sterile in spite of the open communication which exists between the common duct and the intestinal tract.[60] The current of flow carries foreign material into the intestines, and, even though

[60] E. Fraenkel and Krause, Ztft. f. Hyg., vol. xxxii p. 97.

bacteria are artificially introduced into the bile, they may be carried away by the current without their doing any harm. On the other hand, a mere ligation of one of the larger bile-ducts in an animal often suffices to set up an inflammation.[61] (The following facts support the view that infections of the biliary tract enter by way of the portal vein more frequently than by the common duct. Adami and Ford have claimed that there is a constant passage of bacteria through the mucosa of the healthy intestines; and bacteria introduced into the blood may be excreted in the bile (Cushing). The bacteria causing a cholecystitis are often not those commonly found in the duodenum. The infection of the biliary passages above a ligature around the common duct could hardly come from an ascending infection. Finally, if an enteritis be caused by the administration of arsenic, etc., and if the animal then be fed some easily recognized organism, such as the bacillus prodigiosus, this organism can often be demonstrated in the bile-passages. These facts render it very probable that infection of the bile-passages frequently takes place by way of the portal vein. —Ed.) The bile is apt to contain bacteria in the infectious diseases, such as typhoid fever and pneumonia.

The bacterial infection produces an inflammation of the mucous membrane and a desquamation of its epithelial cells. These latter contain undissolved cholesterin. They likewise contain calcium salts, and these probably react to form the insoluble calcium salt of bilirubin. From this salt, as well as from the amorphous cholesterin in the cells, the biliary calculus takes its origin. Its further growth is carried on by the deposition and recrystalization of new material, especially of cholesterin.

Several facts favor the view that gall-stones result from infectious catarrhs of the biliary passages. Thus bacteria may be recovered from the centres of gall-stones, although this

[a] Homen, Ztrbl. f. Path., vol. v. p. 825.

is possible only in the minority of cases. Gall-stones have also been produced experimentally, by causing biliary stasis and by infecting the bile-passages with bacteria of low virulence. As we have already stated, groups of stones in a gall-bladder are frequently of about the same size and presumably of the same age, and it may be inferred that they have all originated at about the same time from a common cause. Infection of the bile-passages is by no means an infrequent event after certain infectious diseases, especially after typhoid fever, and it is quite conceivable that this furnished the common cause for the formation of a number of stones, and that afterwards the bacteria died out of the bile and no new stones were formed.

Cholelithiasis frequently produces no symptoms; and especially is this so when the calculi lie quietly in the gall-bladder without occluding any of the ducts. Gall-stones may, however, give rise to severe pains, as well as to inflammations, peritoneal adhesions, perforations, and septic infections of the liver. All of these evil consequences are initiated by an inflammation of the gall-bladder containing the stones. Riedel believes that this inflammation may be induced merely by the presence of the stone which acts as a foreign body, but that in some cases at least it is started by a traumatism. The cystic duct is then liable to become occluded either by the extension of the inflammation to its mucous membrane or by the lodgement of a stone within it. Hydrops of the gall-bladder ensues. Its original contents of bile become modified by interchange with the lymphatic fluids. The cholates early disappear, the pigments follow them, and finally a clear fluid is left, which contains salts, cholesterin, neucleo-albumin, and characteristic proteids. If bacteria are present, they may cause suppuration. The inflamed wall of the gall-bladder may ulcerate, it may become adherent to surrounding structures, or it may perforate. Not infrequently the stone passes

through the cystic duct and occludes the common duct. It may then produce a variety of inflammatory processes in the liver, the peritoneum, the stomach, and the intestines.

The stagnation of bile and the injury to the walls of the biliary passages, both common results of gall-stones, greatly favor the development of secondary infections. We have already stated that bacteria may enter the common duct from the duodenum, but that they probably more frequently descend from the liver, whither they have been carried by the portal blood. The obstruction caused by the stones greatly favors the multiplication of bacteria which have thus entered the bile, and inflammatory processes of all kinds result.

Carcinomata sometimes complicate gall-stones, and in such cases it is supposed that they are caused by the irritation of the mucous membrane.

Biliary colic is the most frequent manifestation of cholelithiasis. It is characterized by attacks of violent pain in the region of the liver, and is usually accompanied by vomiting, fever, and sometimes by jaundice. The paroxysm may last for hours or days. The colicky pains are caused by the inflammation and distention of the tract and by the spasmodic contractions of the muscle in the gall-bladder and ducts. In a certain number of cases the attack is precipitated by the passage of a small stone from a wide into a narrow passage, as happens at the exit from the gall-bladder or just before the entrance into the duodenum. Yet such is not always the case. A gall-bladder which contains large stones and which is isolated by an old occlusion of its duct is not infrequently the seat of colic. Indeed, colic may come from a gall-bladder which contains no stones and which is merely shrunken and surrounded by adhesions. The immediate cause of the paroxysm of biliary colic is frequently an inflammation of the bile-passages. This may either drive the stone into a narrower portion of the duct, or it may cause the mucous membrane to

swell about the stone, thus occluding the passage. The fever and jaundice that so often accompany biliary colic will be discussed in another place (p. 273).

The Exclusion of Bile from the Intestines.—The bile may be excluded from the intestines by gall-stones lodged in the common or hepatic ducts, by tumors growing within them or pressing upon them from without, or, finally, by catarrhal inflammations which cause a swelling of the mucous membrane, and so occlude the narrower portions of the passages, especially the exit of the common duct at the papilla of Vater and the smaller bile capillaries within the liver.

The effect of an occlusion of the common duct varies with the site of the obstruction. If the latter be seated high up, then bile alone is excluded from the intestines, whereas, if it be at the papilla of Vater, the pancreatic juice may also be in part or altogether shut off. Experiments upon dogs have shown that, when no bile can enter the intestines, the digestion and absorption of proteids and carbohydrates proceeds approximately in a normal manner, whereas the absorption of fats is seriously interfered with; only about forty per cent. of the fat taken in the food being absorbed, as compared to the normal of ninety per cent.[62] Fr. Müller has shown that the same relations hold good for man. If bile be excluded from the intestines, the absorption of carbohydrates is not effected and the absorption of proteids is only slightly lessened; whereas, on the other hand, from sixty to eighty per cent. of the fat taken in the food escapes absorption as compared with the normal of from seven to eleven per cent. The "clay color" of the stools in these cases is caused partly by the absence of bile pigments and partly by the presence of excessive quantities of fat. It is difficult to explain the cause of this diminished absorption of fat on the theory that the latter is taken up

[62] Voit, Beiträge z. Biol., Stuttgart, 1882; Rohmann, Pflüger's Arch., vol. xxix. p. 509.

from the lumen of the intestines as fine particles. If, however, we assume that it is absorbed in a state of solution after having undergone hydrolytic cleavage,[63] then the important rôle played by the bile might be in part explained by the fact that the cholates are capable of holding large quantities of fatty acids in solution.[64]

(The bile may also assist the digestion and absorption of fats in other ways. In the first place, the emulsification of fats is favored by the presence of bile; and in the second, the bile accelerates the fat-splitting action of the pancreatic juice eightfold and even more.[65] There appears, therefore, to be a sufficient physiological explanation for the effect which follows an exclusion of the bile from the intestines.—Ed.)

Even though the bile be excluded from the intestinal tract, it is possible to maintain nutrition by paying sufficient attention to the diet, which should, under these circumstances, consist mainly of proteids and carbohydrates. If the food contains much fat, then the latter undergoes excessive cleavage through the action of the pancreatic juice and of the intestinal bacteria. The products of this decomposition irritate the intestinal mucous membrane, and so may lead to disturbances of its functions. For this reason the administration of fats to patients with biliary obstruction is not only useless but frequently injurious. We are not yet certain what effect the absence of bile exerts upon the bacterial decompositions, which normally take place in the intestines. The putrefaction of proteids has been found to be increased in some instances,[66] whereas in others it has been diminished.[67] It is very doubtful if the bile exerts any antiseptic action upon the growth of micro-organisms in the

[63] Altmann, His. Arch., 1889, p. 91; Krehl, ibid., 1890, p. 97; Pflüger, Pflüger's Arch., vol. lxxxviii. pp. 299, 431; vol. xc. p. 1.

[64] Matthes and Marquardsen, Kongr. f. in Med., 1898, p. 358.

[65] Hewlett, Johns Hopkins Bull., January, 1905.

[66] Brieger, Ztft. f. klin. Med., vol. iii. p. 465.

[67] Müller, Ztft. f. klin. Med., vol. xii. p. 45.

intestines, for Strasburger [68] found no increase, and even a diminution, in the number of bacteria in the fæces in cases of complete biliary obstruction.

Jaundice.—If the lumen of the common duct be obstructed, and if the liver cells continue to secrete bile, then the gall-bladder and the bile-passages become filled with the secretion, the pressure of the bile within them increases, the liver cells are forced apart, and the bile is absorbed into the lymphatic system or directly into the blood.[69] It thus enters the general circulation and permeates all the organs of the body. The liver cells may, indeed, resecrete some of the constituents out of the blood; yet this has little effect, for, the passage into the intestines being obstructed, these constituents are again reabsorbed.

'In jaundice the bile pigments are deposited in various tissues, and the skin assumes a color which varies from a light yellow to a dark green or brown. Whether these different shades are due to a blending of varying amounts of bile pigments with the color of the skin, or whether they arise from a conversion of bilirubin into other pigments, has not been decided. The jaundice may be visible within a few hours after the obstruction has taken place, though usually it does not appear for from one to three days. The retained bile pigments are excreted by the kidneys and by the sweat-glands; but they do not, as a rule, appear in the tears, the saliva, or the gastric juice.

Of the constituents of the bile which pass into the lymph and the blood, the bile salts are of especial interest on account of their known toxic properties. During the first few days of jaundice they can frequently be detected in the urine, but in the later stages they are usually absent. Concerning the quan-

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[68] Strasburger, Ztft f klin. Med., vol. xlvi. p. 432.

[69] Gerhardt, Kongr. f. in. Med, 1887, p. 460, Harley, Du Bois' Arch, 1893, p. 291.

titative relations of other constituents of the bile, how much are formed, how much eliminated in the various secretions, and how much are destroyed in the body, we know but little.

Jaundice may arise not only from an obstruction to the flow of bile through the larger passages, but from obstructions located in the smaller biliary capillaries. These produce the jaundice which may accompany various diseases of the liver, such as cirrhosis, carcinoma, cholangitis, and calculi of the finer ducts. The development of jaundice is dependent less upon the nature of the disease than upon its location, the essential factor being an obstruction to the exit of bile. The jaundice that so frequently accompanies gall-stones may be due to the lodgement of a stone in the common or hepatic ducts, or to an associated inflammation of the mucous membrane. According to Riedel, the latter is the more common. Closure of the cystic duct does not ordinarily cause jaundice.

The resorption of the stagnating bile is influenced not only by the degree of mechanical obstruction, but by the consistency of the secretion. A thick viscid bile, rich in pigments, may be reabsorbed even when the obstruction is a comparatively slight one, such as might be caused, for example, by a catarrh of the bile passages or by an enlargement of degenerated liver cells. The icterus of phosphorus and of toluylendiamin poisonings is usually produced in this manner, as is that which may accompany snake-bites, pneumonia, pyæmia, septicæmia, and various other intoxications and infections. In none of these can a marked obstruction to the outflow of bile be demonstrated. This fact gave rise to the theory that the jaundice in such cases does not depend upon the changes in the liver, but upon the formation of biliary pigments in other parts of the body. It is, indeed, possible for bilirubin to be formed outside of the liver, for this happens in old blood-clots; yet the amount, thus formed, is very small and never produces jaundice. Indeed, we may say that, so

far as we know, jaundice is always of hepatic origin, and that we have no proof that a "hæmatogenous" jaundice can occur. For example, it is impossible to produce jaundice in birds after extirpation of the liver.[70] Furthermore, it has been shown that jaundice of the typical "hæmatogenous" type may be accompanied by the appearance of the bile salts in the urine, a proof that the liver was involved in the condition.[71] That these salts may be absent in certain cases proves nothing in this regard, for the quantity of bile salts formed under different conditions varies greatly, and it is apt to be especially small during jaundice. Finally, it has been demonstrated that an extensive destruction of red blood-corpuscles may lead to a swelling of the hepatic cells, and so to an obstruction of the finer bile-passages.

Many observers incline to the belief that jaundice is always due to such an obstruction to the exit of bile, although it must be admitted that in many instances the obstruction is more or less hypothetical and cannot be demonstrated. Another explanation for these cases has been advanced,—viz., that the liver cells pour their secretion directly into the blood or lymphatic systems.[72] It is important that more attention should be paid to possible changes in the liver cells in these cases.

The cause of the icterus neonatorum which occurs in about sixty per cent. of all new-born children is not well understood. This much is certain, that it results from the resorption of bile; for not only the pigments, but the bile salts as well, are found in the various body fluids.[73] It seems probable also that icterus neonatorum is associated with a destruction of the red

[70] Minkowski and Naunyn, Arch. f. exp. Path., vol. xxi. p. 1.

[71] Naunyn, Arch. f. Anat. u. Physiol., 1868, p. 401.

[72] Minkowski, Kongr. f in. Med., 1892, p. 127; ibid., Ergebnisse der Path., 1897, vol. ii. p. 705.

[73] Birch-Hirchfeld, Virch. Arch., vol. lxxxvii. p. 1.

blood-corpuscles, for it is especially apt to develop in those infants who have had the cord tied late and who have therefore received a larger amount of blood from the placenta. We know that jaundice frequently accompanies an increased destruction of red blood-corpuscles, as happens in paroxysmal hæmoglobinuria, but the attempts to produce it experimentally by the introduction of hæmoglobin have hitherto failed. There seems, therefore, to be some other factor present than the mere destruction of the erythrocytes. Possibly, as Quincke believes, the jaundice of the new-born is due to the resorption of bile from the intestines. This theory receives some support from the fact that for several days after the birth the blood from the intestines may not go through the liver, but may pass directly into the general circulation from the portal vein by way of the ductus venosus.

Effects of Jaundice.—The obstruction to the flow of bile may cut off this secretion from the intestines, with the results which have already been described (p. 271). On the other side, the liver cells are affected. They become compressed and separated; and, though for a time they may continue to perform their functions normally, nevertheless, after a while, they suffer both in structure and in function. Areas of necrosis and inflammation may appear.[74] These are due in part to the toxic action of the bile itself, in part they are due to the infections that are so prone to appear in stagnating bile. It is impossible to apply the experimental data upon this subject to man, because the various animals differ so greatly in the effect produced by a stasis of bile upon the liver.

It is difficult to decide which constituents of the bile produce each of the varied general symptoms of jaundice. The cholates seem to be the most toxic in their action, although recently attention has been directed to the poisonous properties

[74] Beloussow, Arch. f. exp. Path., vol. xiv. p. 200; Gerhardt, ibid., vol. xxx. p. 1.

of the biliary pigments.[75] The itching of the skin so frequently present is apparently due to the deposit of pigment in the skin. In the early stages of jaundice the heart's action may become slow and irregular, both in force and frequency, and the blood-pressure may fall (see p. 84). These symptoms seem to be due to the action of the bile salts, for even small doses of sodium cholate stimulate the central endings of the vagus nerve, and larger doses act upon the heart itself. The convulsions that very rarely occur in the beginning of jaundice are also possibly due to the action of the bile salts, for the injection of very large amounts of cholates will produce convulsions. True cholate intoxication occurs in man only when the obstruction to the outflow of bile is complete or nearly so, and when the formation of these salts is not materially interfered with. It may accompany catarrhal jaundice, cholelithiasis, and carcinomatous obstruction. Yet the cholate symptoms are by no means always present in jaundice and often they last only a short time, for the quantity of bile salts in the blood varies enormously, and it is usually small in the later stages of an obstruction.[76] This is due apparently to the fact that the hepatic cells may lose, more or less, their ability to produce the bile salts, as well as to the constant endeavor on the part of the liver to remove bile salts from the blood. For these reasons there are frequently no signs of cholate intoxication, even when the jaundice is most profound.

Other Hepatic Toxæmias.—At times serious toxic disturbances develop in the later stages of liver disease, and these may or may not be accompanied by jaundice. The patient becomes stuporous and delirious, and, after a few days of high fever and perhaps convulsions, death usually terminates the scene. The condition resembles the termination of certain

[75] Stadelmann, Ztft. f. Biol., vol. xxxiv. p. 57.
[76] Yeo and Herroun, Jour of Physiol., vol v. p. 116; Stadelmann, loc. cit.

other metabolic diseases, such as the coma of diabetes and the uræmia of nephritis. It is very improbable that these late toxic symptoms are in any way caused by a resorption of bile, for, in the first place, the picture differs from a cholate intoxication in the high fever and in the frequency of general convulsions; and in the second place, diseases of the liver may terminate in this manner even though hardly any jaundice is present, and even though, furthermore, on account of the extensive destruction of hepatic cells, it is probable that only very small quantities of the bile salts are manufactured.

A wide-spread degeneration of the liver cells seems to be the underlying cause of these toxæmias. The hepatic cells are known to perform very important metabolic functions, such as the storing of carbohydrates, the formation of urea out of ammonium salts, the conversion of toxic aromatic compounds into the comparatively harmless ethereal sulphates, and the disposal of various other poisons absorbed from the intestines. It may therefore be easily understood how seriously the metabolism might suffer when the liver is thrown out of function. Possibly the above toxæmias are caused by poisonous compounds which would normally be rendered non-toxic in the liver. Of great interest in this connection is the fact that geese will frequently die of convulsions after extirpation of the liver, if they are fed on a rich nitrogenous diet.[77] The same holds true for dogs if an Eck fistula between the portal vein and the inferior vena cava [78] permits the blood to flow from the intestines directly into the general circulation without traversing the liver, under which circumstances the liver cells gradually degenerate. Certain symptoms, presented by these animals, would seem to be due to the action of carbamic acid. If ammonium carbamate be injected into the portal blood of

[77] Minkowski, Arch. f. exp. Path., vol. xxi. p. 41.
[78] Hahn, Massen, Nencki, and Pawlow, Arch. f. exp. Path., vol. xxxii. p. 161.

normal animals, it is converted into urea in the liver. In animals from which the liver has been extirpated or thrown out of function this does not occur, and in them the carbamic compounds would be free to produce toxic symptoms.

The toxæmia associated with extensive hepatic disease may also possibly be due to the formation of poisonous compounds from the disintegrating liver cells. Finally, some of these intoxications are undoubtedly of infectious origin, as is probably the case in acute yellow atrophy [79] and in the not infrequent infections of the biliary passages which follow chronic obstruction.

THE PANCREATIC JUICE.

The complete exclusion of the pancreatic juice from the intestines without a concomitant exclusion of bile is extremely rare, for the gland usually possesses two functioning ducts.[80] A closure of both of these is rare, and a total degeneration of the secreting glandular parenchyma is likewise very exceptional. By far the most frequent site of a pancreatic obstruction is the papilla of Vater, and here not only the duct of Wirsung, but the common bile-duct as well, would be closed. One can never be certain as to the condition of the duct of Santorini in man, for it is normally open in about two-thirds of all cases,[81] and it may be closed by a catarrhal process extending into it from the duodenum.

For these reasons we are insufficiently acquainted with the results of a simple exclusion of the pancreatic juice from the intestines. F. Müller [82] studied the fæces of several patients who had extensive pancreatic degeneration, and found that the absorption of carbohydrates in the digestive tract was not at all affected by the disease, that the absorption of the proteids

[79] v. Noorden, Pathologie des Stoffwechsels, p. 275.
[80] Opie, Diseases of the Pancreas, p. 30.
[81] Opie, loc cit.
[82] Ztft. f. klin. Med., vol. xii. p. 45.

was only slightly effected, and that the total quantity of fats absorbed was likewise not far from the normal. The cleavage of fats in the intestines, however, was considerably diminished; for, of the fat in the fæces, only forty per cent. was found to be split into fatty acids and soaps as against the normal of about eighty-four per cent. (Others have found that pancreatic disease greatly lessened the absorption of fats from the intestines. Thus Weintraud's patient lost from twenty-two to twenty-five per cent. of the fat taken in the food, and Deucher's two patients lost respectively 52.8 and eighty-three per cent. of the fat taken in the food.[83] These losses considerably exceed the normal of seven to eleven per cent. In regard to the extent of cleavage of the fats in the fæces, the results have also been somewhat contradictory. While some have found, as did Müller, that the cleavage was markedly less than normal, others have found but little change.[84]

In some cases of pancreatic disease large quantities of nitrogenous material have passed through the intestines unabsorbed, and the microscopic examination of the fæces has shown undigested muscle-fibres in great abundance. In the absence of very serious intestinal disease, the presence in the stools of large numbers of fat droplets and of an excessive amount of undigested meat-fibres is certainly very suggestive of an exclusion of pancreatic juice from the intestines.—ED.)

The experimental studies of Abelmann have demonstrated the serious impairment of absorption which follows the extirpation of the pancreas of animals.[85] About fifty-six per cent. of the ingested proteids, twenty to forty per cent. of the carbohydrates, and all of the non-emulsified fats appeared in the fæces. Of the latter, from thirty to eighty-five per cent. had

[83] Cited in Schmidt-Strasburger, Fæces des Menches, Berlin, 1901, p. 149.
[84] See Schmidt-Strasburger, loc. cit.
[85] Abelmann, Diss. Dorpat.

undergone cleavage into fatty acids and soaps. If the fat were introduced in the form of a natural emulsion, such as milk, then a considerably larger proportion, about thirty to fifty per cent., was absorbed by the intestines. Other experimenters have obtained quite different results; in many cases the fat was not absorbed at all, and in others up to eighty per cent. was absorbed.[86] It seems to me that the results of these experiments cannot be applied directly to human pathology for extirpation of the pancreas is attended with considerable shock to the animal and we have no data as to how the secretion of bile is influenced by these operations. The metabolism of carnivora should be studied after the pancreatic ducts have been tied. The fact that the administration of the pancreas of a pig to these animals increases the absorption of food would seem to indicate that the absence of pancreatic secretion is the main cause of their insufficient absorption.

(Fat Necroses.—In many pancreatic diseases, peculiar opaque, whitish spots have been noticed, which were most numerous in the immediate vicinity of the pancreas and beneath the peritoneum, but which may also be found in other distant parts of the body. These whitish spots are caused by a decomposition of the fat in the adipose tissue into fatty acids and glycerin. The latter, being soluble, can be washed away; whereas the fatty acids are deposited in typical needles, which later, combining with calcium, give irregular granular masses.[87] This abnormal cleavage of fat in the tissues appears to be due to the escape of pancreatic juice from the pancreas, for the injection of pancreatic extracts into the tissues has been followed by typical fat necroses, and the ordinary fat necroses contain a fat-splitting enzyme in greater quantity than does normal fatty tissue.[88] Indeed, this enzyme may even appear

[86] See Oser in Nothnagel's system.
[87] Langerhans, Virch Arch, vol cxxii p. 252.
[88] Flexner, Jour of Exp. Med., vol. ii. p. 413.

in the urine after extensive experimental destruction of the pancreas.[89]

Fat necroses are usually most numerous in those conditions in which a rapid destruction of pancreatic tissue has taken place, as in acute hemorrhagic pancreatitis. They are also frequently quite numerous after obstruction of the pancreatic duct. Finally, a few small necroses may not infrequently be found within the tissues of the normal pancreas. Yet, so far as we know, extensive necroses do not occur without there being some lesion of this gland.

Relation of the Bile to Pancreatic Disease.—Owing to the fact that the common bile-duct and the main pancreatic duct usually open in common into the diverticulum of Vater, which latter then opens into the duodenum, it is possible for the bile to enter the pancreas directly from the common duct when the exit into the duodenum is obstructed. Such an obstruction has been produced by a small gall-stone, which was large enough to close the opening into the intestines, yet small enough not to fill up the diverticulum completely.[90] Bile is certainly very irritating to the pancreas, and its entrance into that gland may be followed by an acute hemorrhagic inflammation.[91] In other cases, when the irritation is less marked, a chronic pancreatitis may result.—Ed.)

THE PROCESSES IN THE INTESTINES.

The Effect of Poisons upon the Intestines.—The intestines may be injured by various substances, such as the fatty acids, the metallic salts, aromatic compounds, etc. Many of these are used therapeutically, while others may be taken in the food. It is not easy to separate those which are toxic from those which are not, for the susceptibility of different

[89] Hewlett, Jour. of Med. Research, vol. ix. p. 377.
[90] See Opie, Diseases of the Pancreas, p. 40.
[91] Opie, Johns Hopkins Hosp. Bull., vol. xii. p. 182.

individuals varies enormously in this respect. Even such a marked poison as arsenious acid, which in most men causes a violent enteritis, may become comparatively harmless through habit, and quantities may then be borne which would ordinarily be almost immediately fatal.

Toxic substances may be elaborated outside the body by the action of bacteria. These include the so-called ptomaines, many of which, such as neurin, mydalein, and mytilotoxin, are extremely poisonous.[92] Since such compounds are only formed in the later stages of putrefaction, an intoxication from this source is most apt to follow the ingestion of decomposed food. Some of these poisonous substances injure the wall of the intestines, producing anatomical and functional disturbances, while others are absorbed and produce more general symptoms.

(Specific toxins, elaborated by specific bacteria, may be introduced with the food. The poisonings which sometimes follow the ingestion of milk, cheese, and meat seem to be of this character. A specific meat intoxication, so-called botulism, has been shown to be caused by the toxin formed by a definite anaërobic bacillus,[93] and an antitoxin has been produced which will neutralize its effect.—ED.)

It is often difficult to determine whether a certain intoxication resulted from poisons introduced with the food, or whether it arose from toxins which were produced within the intestines by the abnormal action of bacteria; yet in some instances the former is by far the more probable, for the symptoms appear almost immediately after the ingestion of the decomposed food. The same is also true when the intoxication is caused by cooked material, for it is then very improbable that any living organisms other than spores were introduced.

[92] Brieger, Ueber Ptomaine, Berlin, 1885–86; Neumeister, Physiol. Chem., second edition, p. 268.

[93] Van Ermengen, Ztft. f Hyg., vol. xxvi. p. 1.

Abnormal Bacterial Processes within the Gastro-Intestinal Tract.—Numerous bacteria are regularly carried into the stomach with the food. A portion of these are there destroyed, some are reduced in virulence, and a part passes on, but slightly injured, into the duodenum. When many bacteria reach the intestines, some may decompose the carbohydrates or split the fats, thus producing organic acids even in the small intestines. To what extent the proteids undergo putrefaction in the upper intestines under pathological conditions is not known. In the lower ileum, and especially in the colon, the bacterial decompositions normally become more marked, and here the putrefaction of the proteids is a normal process.

The number of bacteria in the human intestines varies greatly.[94] The dried fæces of a healthy man are made up of about one-third, by weight, of bacteria. Yet the upper small intestines in fasting animals, at least, are almost free of micro-organisms,[95] and it seems very probable that they regulate their bacterial flora to a certain degree.

Certain factors seem to inhibit bacterial growth in the small intestines. As we have seen, the hydrochloric acid of the stomach diminished the number of bacteria present in the food, and it is probable that the bile acids, the fatty acids produced by cleavage of the fats, and the intestinal secretions themselves exert a certain antiseptic action in the upper intestines. Of greater importance, however, is the rapid transit of material through the duodenum and ileum, and the few hours that food remains there does not allow sufficient time for the bacteria to multiply. Fortunately, in the large intestines, where the transit is slower and where the bacterial action is

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[94] Strasburger, Ztft. f. klin. Med., vol. xlvi. p. 413; vol. xlviii. p. 491.

[95] Kohlbrugge, ref. in Baumgarten's Jahresber., 1901, 895; see, also, Cushing and Livingwood, Contributions to the Science of Medicine, by the pupils of Dr. W. H. Welch, Baltimore, 1900, p. 543.

most marked, the greater portion of nutritive material has already been absorbed, and the bacteria have less to decompose.

Another protection against the growth of strange bacteria in the intestines is the inhibitory action which the normal flora seems to exert upon the growth of outsiders.[96] For this reason the normal flora of the intestines is probably very useful. Whether it is absolutely necessary or not, has received different answers from different investigators.[97] Guinea-pigs may be reared upon sterilzed milk, but a similar attempt with chickens has failed, which fact appears to support the view that the presence of micro-organisms in the gastro-intestinal tract is necessary during extrafetal life.

The kind of micro-organisms in the intestines depends partly upon the food taken, and partly upon the general condition of the individual. The intestinal contents of a newborn infant are sterile, but after birth they quickly become infected, and at the end of the fourth day a fully developed intestinal flora is present. The latter varies with the kind of food used, whether mother's or cow's milk, and it varies with each change in the food in later life.

So long as the epithelium remains intact and healthy the body is fairly well protected from invasion by the bacteria which happen to be present in the intestines.[98] The epithelial cells form a protective bulkhead, and their antibacterial action is attributed by some authors to their content of nucleinic acid and its combinations, which substances are acid in reaction and will cause a precipitation of proteids.[99] Yet the protection

[96] Bienstock, Die med Wochens., 1901, Nos 33 and 34; ibid., Annales de l'Institut Pasteur, vol. xiv. p 750, Arch f Hyg, vol xxxix p. 390.

[97] Thierfelder and Nuttall, Ztft. f phys. Chem, vol xxi p. 109; vol. xxii, p. 62; Schottelius, Arch. f. Hyg, vol. xlii, p 48, Metschnikoff, Annales Pasteur, 1901, p. 631, Kijanitzka, Virch Arch, vol. clxii, p. 515

[98] Schott, Ztrbl. f. Bacteriol, vol. xxix I, pp. 239, 291.

[99] Klemperer, Deut med Wochenschr., 1894, No. 20; H. and A Kossel, Du Bois' Arch., 1894, p. 200

afforded to the body by the intestinal mucosa is not an absolute one. Apparently the tubercle bacillus may penetrate the intact mucous membrane, and slight lesions will certainly render the epithelium permeable to many bacteria.[100]

The soluble products of bacterial action frequently pass through the normal mucosa, and in doing so they may possibly render an important service to the individual by immunizing him against the action of the bacteria from which they are derived. Those toxins which are of a proteid nature may in many cases be digested in the intestines, just as are other proteids; yet it would appear that this does not occur in the intestines of infants.[101]

Many intestinal diseases, perhaps the majority of them, are due to abnormal bacterial action within the intestines. The bacteria ordinarily present may increase in number or in virulence, or bacteria that are not usually present may give rise to pathological changes. Such foreign micro-organisms must of course be introduced from without, and it is manifestly impossible, for example, to acquire cholera at a time when no cholera bacilli are about. The mere introduction of pathogenic bacteria does not, however, necessarily do any harm; for just as large numbers of harmless bacteria daily enter the gastro-intestinal canal and there disappear, so may pathogenic organisms be destroyed without their producing any ill effect. They succumb to the various protective agencies in the stomach and intestines that have already been described. In some cases, however, the bacteria introduced are so numerous or so virulent that they cause the disease in practically every individual in whom they enter, as is illustrated by the fact that every person who has partaken of a particular dish may become ill from it.

It is often impossible to say in what manner the infection

[100] Posner and Cohn, Berl. klin. Wochenschr., 1900, No. 36.
[101] Behring, Naturforscher-versammlung zu Kassel, 1903.

has taken place, whether it is by overcoming the normal inhabitants of the intestines, or by causing a lesion of the mucosa, etc. Apparently different factors enter into consideration in different infections. We know, for example, that the cholera vibrio is extremely sensitive to the acid reaction of the gastric juice, and clinical experience has shown that the disease is especially apt to attack individuals who have presumably a lessened gastric acidity, caused either by some slight digestive disturbance or by great fear of contracting the disease.

Intestinal indigestion is apt to be produced in some individuals by certain articles of diet, and it is quite possible that these articles allow the bacteria normally present in the intestines to proliferate with abnormal rapidity, or that they reduce the resistance which the flora of the intestines normally exerts against foreign invaders. In some cases, however, they cause the indigestion by directly influencing the secretions poured into the intestinal canal. The first of these possibilities seems to be exemplified in the case of infants, for in them some very slight qualitative or quantitative change in the food may induce a dangerous proliferation of bacteria, quite independently of the bacterial contents of the food ingested.

On the other hand, the abnormal bacterial growth may follow changes in the secretory or motor functions of the intestines. The normal emptying of the fæces is one of the most important means by which abnormal bacterial growths are limited, and changes in the secretions are perhaps of equal importance.

How frequently the normal inhabitants of the intestinal tract produce disease has not yet been fully determined. It is certain that they may give rise to a peritonitis when the bowel ruptures or when its wall becomes abnormally permeable, as happens in strangulation. Local infections may take place when the intestinal wall is injured, and this is the probable cause of many a colon bacillus cystitis. Beyond this we know

little about such enterogenous autoinfections.[102]   (Generalized infections with the colon bacillus have, however, been frequently demonstrated by blood-cultures.—ED.)   Possibly some of the infantile diarrhœas are caused by a change in virulence in the normal intestinal flora.   (These diarrhœas are now believed to be produced by infections with the dysentery bacillus, although the question as to whether such bacilli may be normal inhabitants of the intestines or not has not yet been fully determined.[103]—ED.)

An abnormal growth of bacteria in the intestines may harm the body in several ways.   Either the poisons formed may be absorbed and cause a general toxæmia, or they may act directly upon the mucosa itself, and so interfere with its functions.   Frequently the mucosa undergoes anatomical alterations, such as degenerations of the epithelium, inflammations, and ulcerations.   These latter are important, for when they occur, the barriers to invasion are let down and bacteria may penetrate the mucosa and cause a general infection.

Various toxic compounds result from bacterial decompositions in the bowel.   Of these, some, such as lactic acid, butyric acid, and acetic acid, have already been mentioned in speaking of the abnormal fermentative processes in the stomach.   These acids are regularly produced in the small intestines, but under pathological conditions the quantity so produced may be enormously increased.   They irritate the intestines, increase the peristaltic movements, and may cause lesions of the epithelium.   Gases, such as hydrogen, carbon dioxide, and methane, likewise may be produced in excessive quantity and cause tympanites and intestinal colic.

An excessive proteid decomposition in the intestines gives rise to all the various products of putrefaction, among them

[102] F. Müller, Kongr. f. in. Med., 1898, p. 156.

[103] Studies from the Rockefeller Institute for Medical Research, vol. ii., 1904.

indol, skatol, phenol, and other compounds belonging to the aromatic series of compounds. Many of these are rendered non-toxic after absorption, through combination with sulphuric acid, glycocoll, glycuronic acid, etc. These combinations apparently take place in the liver, and the compounds, thus formed, are excreted by the kidneys. These aromatic bodies are normally formed almost exclusively in the large intestines. Their amount depends upon a variety of factors, of which the most important are the quantity of material in the chyme that can undergo putrefaction, the amount of substances present which will exert an antiseptic action, the varieties of bacteria present, and the rapidity with which the material passes through the intestines.

(Our best index of the amount of putrefaction which is taking place in the intestines is the quantitative determination of the ethereal or aromatic sulphates in the urine; for, as has been said, the aromatic products of putrefaction are largely eliminated as such sulphates, when once they have been absorbed from the intestines. In this regard, it is important to know not only the absolute amount of these ethereal sulphates in the urine, but also the ratio which this amount bears to that of the ordinary, preformed, inorganic sulphates. In fact, this ratio is regarded by most authors as a better index of the amount of putrefaction than is the absolute quantity of ethereal sulphates excreted. In adults, on a mixed diet, the ratio of the ethereal to the preformed sulphates in the urine varies from about 1 : 10 to 1 : 16, while under pathological conditions this ratio may become 1 : 7 or 1 : 5, or even to 1 : 1.[104] Ethereal sulphates may, however, be formed by putrefactive processes outside of the intestines, especially when there is suppuration without free drainage, and they may also arise from certain drugs of an aromatic nature, such as benzosol, salol, salophen, creosote, etc.

[104] See Herter, Lectures on Chemical Pathology, p. 202.

The mere ingestion of a large amount of material that can putrefy—*e.g.*, a large meat meal—is apt to be followed by an increase in the absolute and relative quantities of the ethereal sulphates in the urine. A similar increase is often observed in catarrhal enteritis. The greatest increase, however, follows stasis of material in the intestines. Ordinary constipation is often associated with a more or less marked increase, and intestinal obstruction is regularly associated with the elimination of large quantities of ethereal sulphates in the urine.

We do not know how serious the absorption of these aromatic bodies from the intestines is. Indol, when administered by mouth, is only moderately toxic, and individuals vary considerably in their susceptibility to its action. Small doses are liable to produce frontal headaches and a condition of nervous irritability and restlessness, larger doses may cause diarrhœa, or marked irritability, insomnia, and mental restlessness. The continued administration of enough indol to cause a constant and decided reaction for indican in the urine is capable of inducing neurasthenic symptoms.[105] It is very probable therefore that the neurasthenia which is so often seen in cases of chronic intestinal indigestion is in part due to the absorption of the aromatic products of putrefaction.—Ed.)

It is also possible that the nephritis which so frequently follows intestinal obstruction is caused by the products of intestinal decomposition.[106]

Other poisons of a more complex nature than those we have just mentioned may play an important rôle in some cases of intestinal intoxication.[107] Apparently ptomaines are not formed in the intestines very frequently, and in most infectious diseases they do not appear in the urine,[108] yet they have been

[105] See Herter, loc. cit., p. 212.
[106] Frank, Berl. klin. Wochens., 1887, No. 38.
[107] See Kongr. f. in. Med., 1898.
[108] Baumann and Udranszky, Ztft. f. phys. Chem., vol. xiii. p. 562.

found in severe gastro-enteric disturbances. (Cholin is one of the decomposition products of lecithin, and under certain circumstances it may be transformed into the highly toxic substance, neurin. Nesbitt has shown that if dogs with an intestinal obstruction be fed upon the yolks of eggs, rich in lecithin, then neurin and cholin may be found in the intestinal contents,[109] and it is possible that the same may occur in certain pathological conditions in man. Perhaps the toxic symptoms which sometimes follow the eating of eggs are caused by neurin.—ED.) Cystinuria is regularly accompanied by the excretion of the ptomaines, putrescin and cadaverin, in the urine and fæces. In general, however, it would appear that the food does not remain a sufficiently long time in the intestines for ptomaines to be formed.

Toxic intestinal disturbances may arise finally from proteid-like substances and from other compounds of a totally unknown composition.[110] The nature of these is but little known, and in recent times it has been questioned whether any of them are true proteids.

Many disturbances in the function of the intestines have been ascribed to the action of protozoa, though their etiological relationship has been well established for only one disease, endemic dysentery.[111] The virulence of the amœba of dysentery for cats leaves us in no doubt as to its pathogenicity. Yet not all cases clinically classified as dysentery are due to the action of this amœba.

The Pathology of Absorption.—Absorption takes place throughout the small intestines, being more rapid for organic substances at least, in the upper than in the lower portion.

[109] Nesbitt, Jour. of Exp. Med., vol. iv. p. 11.

[110] Brieger and Fraenkel, Berl. klin. Wochens., 1890, No. 11; Neumeister's Physiol. Chem.

[111] Councilmann and Lafleur, Johns Hopkins Hosp. Rep., vol iii.; Kartulis in the Nothnagel System.

According to the most trustworthy observations, but little nutritive material is absorbed by the large intestines.

The manner in which many diseases of the intestines affect the absorption of food is not fully known. Those circulatory disturbances that produce a slower blood-current lead to a diminution in the absorption of fats, but do not affect the absorption of the sugars and proteids.[112] Fat absorption is also reduced whenever the lymphatic vessels that drain the intestines are obstructed, as may happen in tuberculosis of the mesenteric glands. The diseases that affect the intestines only in isolated areas, such as tuberculosis and typhoid fever, have almost no influence upon absorption.[113] On the other hand, wide-spread diffuse diseases of the mucosa, such as enteritis and amyloid degeneration, will diminish the fat absorption if they are moderately severe, and will reduce the absorption of all kinds of food if they are very severe. This loss of material is caused partly by the changes in the mucosa itself and partly by the rapid passage of the food through the intestinal tract, though diarrhœa alone does not necessarily diminish absorption.[114]

In the healthy individual, the greater part of the water in the food is absorbed in the upper small intestines.[115] If the amount of water in the fæces be increased, this may arise, first, from a diminished absorption of water from the food, due either to the presence of salts or other bodies which raise the osmotic tension of the intestinal contents, or to a too rapid passage of the chyme through the intestines. A rapid transit of material through the large intestines always diminishes the absorption of water. Drinking large amounts, on the other hand, frequently has no effect upon the fæces.

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[112] F. Müller, Kongr. f. in. Med., 1887, p. 404; ibid., Ztft. f. klin. Med., vol. xii. p. 45; Grassman, Ztft. f. klin. Med., vol. xv. p. 183.

[113] Müller, loc. cit.; Hösslin, Virch. Arch., vol. lxxxix. pp. 95, 303.

[114] Dapper, Ztft. f. klin. Med., vol. xxxi. p. 382.

[115] v. Mering, Mortiz, Kongr. f. in. Med., 1893, p. 471.

In the second place, an increase in the amount of water in the fæces may result from excessive secretion. We know that the stomach secretes water readily and there is abundant reason to believe that the intestines may likewise furnish large quantities of fluid to their contents, either by the process of transudation or by that of secretion. The most remarkable example of watery fæces is furnished by the " rice-water" stools of Asiatic cholera. These contain only a trace of albumin, an amylolytic enzyme, and hardly any salt except sodium chloride.[116] Their composition approaches that of the normal intestinal secretion, differing from an ordinary inflammatory exudate in the low proportion of proteids present and in the amylolytic ferment. Cohnheim, therefore, believed that the rice-water stools of cholera were caused by an increase in the intestinal secretions, rather than by an inflammatory exudation. Yet later researches have shown that the essential pathological process in cholera is an intense inflammation of the mucous membrane, so that the question as to the inflammatory or secretory nature of the fluid still remains unsettled.

(Another example of watery stools caused by an excessive secretion of fluid is furnished by the fluid fæces which follow the use of saline cathartics. The watery character of these fæces is due very largely to the stimulation of intestinal secretion which results from the absorption of the cathartics.[117]—Ed.)

Disturbances in the Intestinal Movements.—In discussing this subject, it is necessary to consider separately the small and the large intestines, for the peristaltic movements in each are quite different.[118] During complete fast, rest prevails throughout the entire gastro-enteric tract, whereas digestion leads to peristaltic movements of the small intestines. These consist,

[116] Kuhne, Berl. klin. Wochenschr., 1868, p. 170.
[117] J. B. MacCallum, Am. Jour. of Physiol., vol. x. pp. 101, 259.
[118] See Magnus, Pflüger's Arch., vol. cii. pp. 123, 349.

in the first place, of progressive waves of contraction which affect the circular muscle over a limited area, and which travels forward, tending to carry the chyme with them. The second form of movement is produced by a simultaneous contraction of the circular and longitudinal fibres, and this results in a twisting of the intestinal coils, which tends to bring different parts of the chyme in contact with the mucosa. (Cannon describes a third movement,—rhythmical segmentation. At regular intervals simultaneous constrictions in the lumen of the small intestines take place, and these then again relax. These movements occur about thirty times to the minute in cats. They persist during sleep, but are checked by violent emotions. According to the same author, the most frequent movements in the large intestines of cats are waves of antiperistalsis, which begin near the rectum and terminate at the ileo-cæcal valve. Ordinarily these waves pass for a short time at the rate of about five a minute, and then a period of rest lasting about ten minutes intervenes. These antiperistaltic waves cause the contents of the large intestines to be thoroughly mixed.[119]—Ed.)

Defecation is a partly voluntary, partly reflex act, which is initiated by the presence of more or less fæces in the rectum. In many individuals defecation occurs regularly at the same time each day, while in others it occurs very irregularly. In diarrhœa, the large intestines fill rapidly and frequently with fluid contents, and their peristaltic movements are increased. The small intestines, however, may or may not be affected. The milder and more transitory diarrhœas usually do not involve the small intestines, as may be inferred from the character of the fæces. On the other hand, in many conditions, such as typhoid fever, the small intestines are affected and the stools contain undecomposed biliary pigments and abnormal quantities of unabsorbed food material. Finally, a

[119] Cannon, Am. Jour. of Physiol., vol. vi. pp. 123, 249.

catarrh may involve the small intestines almost exclusively, in which case it may or may not be accompanied by a diarrhœa and may even be associated with constipation.

Nervous Diarrhœas.—The cause of the diarrhœa may lie outside of the intestines. In many individuals a mere cooling of the skin or a feeling of nervousness will produce diarrhœa without necessarily disturbing the general health. A gradual transition may be seen in such cases from the physiological to the pathological; in the one, a pronounced stimulus is necessary to produce any effect, whereas, in the other, a little excitement or even the fear of a diarrhœa may be enough to bring it on. Such individuals often show other neurasthenic or hysterical stigmata. It seems probable that their central nervous system affects the peristalsis of the intestines through the vagus and splanchnic nerves. Even normally, the peristaltic movements are influenced to a certain extent by the central nervous system, and in these pathological conditions this influence is greatly exaggerated. In some of these cases, however, the irritability of the intestines themselves may possibly be increased so that they respond excessively to normal stimuli.

Diarrhœas may accompany anatomical diseases of the nervous system, as happens, for example, in the intestinal crises of tabes. It is quite certain that in these cases the diarrhœas are dependent upon changes either in the nerves or in the central nervous system; yet definite proof of this is wanting.

In hysterical girls the small intestines are frequently the seat of increased peristalsis, often giving rise to constant gurgling sounds, without, however, causing any diarrhœa. That these peristaltic movements are dependent upon mental influences is supported by the fact that they are most liable to occur at the very times at which the patient wishes to suppress them.

The watery character of the fæces in nervous diarrhœas

may be due in part to the rapid transit of material through the intestines, though it seems probable that it is more often caused by a nervous hypersecretion from the intestinal mucosa, a condition which would find an analogy in the well-known instances of nervous secretion of saliva, gastric juice, and urine. When the hypersecretion affects the large intestines, the mucus and proteids in the secretion[120] may form tubular and membranous casts, which are afterwards passed in the fæces. This disease, known as colica mucosa (membranous colitis), has, in most instances at least, nothing whatever to do with an inflammation of the mucous membrane,[121] but is a pure secretory neurosis. It usually occurs in nervous women, and may be accompanied by the most violent paroxysms of colic. At times, very similar membranous structures result from true inflammatory processes in the intestines.

Diarrhœas in General Diseases.—Intermediate between these diarrhœas of nervous origin and those due to causes situated within the intestines, is a second group,—viz., those that accompany general diseases. Several possibilities suggest themselves as to the cause of this class of diarrhœas. In the first place, the general disease may so weaken the resistance of the intestinal mucosa that the latter falls a prey to the normal flora of the intestines or to bacteria which are introduced into the gastro-intestinal canal, either by mouth or by the secretions from the infected body. In the second place, toxins produced by the general disease may directly cause the diarrhœa, just as other poisons do. Some infectious diseases, such as pneumonia, rarely cause diarrhœa; whereas others, such as measles, frequently do so. Diarrhœa not infrequently complicates chronic nephritis.

Diarrhœas of Intestinal Origin.—The third and most important class of diarrhœas are those caused by the excessive

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[120] Kitagawa, Ztft. f. klin. Med., vol. xviii. p. 9.
[121] Nothnagel, Diseases of the Intestines, in his System.

stimulation of the intestinal mucosa by the intestinal contents. The materials which act as stimulants are, in the first place, coarse, hard food remnants, especially cellulose, which resist the action of the intestinal secretions and bacteria. In the second place, and more commonly, the peristalsis is excited by chemical irritants, which may either be introduced from without or be produced within the intestinal canal. Of these, we shall only name the organic acids and the gases which result from fermentation.[122] These are of the greatest importance in the production of many diarrhœas. Whether or not water alone will increase the peristalsis has not been definitely settled. We know, however, that diseases which interfere with the absorption of water by the small intestines may lead to diarrhœa, as is the case with amyloid degeneration of the intestines and with the saline cathartics. (Recent work has shown that the saline cathartics act not so much by preventing the absorption of water from the intestines as by directly stimulating its motor and secretory functions. To do this, the cathartic must first be absorbed, and they have been shown to be especially efficient when they are injected directly into the animal's blood, or when they are painted over the peritoneal covering of the intestinal wall.[123]—ED.)

Diarrhœa is favored by an increased irritability of the intestinal mucous membrane, muscle, or nerves, for normal stimuli then give rise to excessive responses. Such an increased irritability of the intestines is probably present in most acute inflammations of the mucous membrane. In acute enteritis, for example, the diarrhœa is due to the combination of two causes, increased intestinal irritability and increased stimulation of the intestines by the products of abnormal fermentations. In chronic enteritis there is frequently no increase in the irritability of the mucous membrane. Even in

[122] Bokai, Arch. f. exp. Med., vol. xxiii. p. 209, and vol. xxiv. p. 153.
[123] MacCallum, Am. Jour. of Phys., vol. x. pp. 101, 259.

intestinal ulcerations the irritability may not be increased, which is especially true of the chronic ulcerations.

The effect of diarrhœa upon the body depends to a great extent upon its cause. If the food is hurried through the upper part of the small intestines, its absorption may be seriously interfered with and the patient may suffer from malnutrition. On the other hand, when the diarrhœa is due entirely to an increased peristalsis of the large intestines, it is often surprisingly well borne, for the most nourishing part of the food had already been absorbed before the large intestines were reached. Other associated conditions, however, may render a diarrhœa most serious. The loss of appetite, the more or less constant pain, and the absorption of abnormal decomposition products,—all these frequently accompany diarrhœas and increase their seriousness.

Constipation.—In constipation the chyme remains in the large intestines for an abnormally long time, and more water is absorbed from it than usual, with the result that the fæces become hard and are passed less frequently than usual. It is impossible to draw any sharp line here between what is pathological and what is physiological. We may say in general, however, that infrequent defecation can only be regarded as pathological when it gives rise to symptoms. Constipation is undoubtedly caused by abnormalities of the large intestines, yet it is unprofitable to speculate on the exact nature of these abnormalities so long as we do not even know why the normal intestines empty themselves so infrequently.

Causes of Constipation. (*a*) *Improper Food.*—In a certain proportion of cases the constipation is caused by improper food. We have stated that the material in the bowels furnishes the normal stimulus to intestinal peristalsis. Every animal must take food that furnishes the necessary amount of stimulus. Thus an herbivora will die of constipation if it be totally deprived of the cellulose which normally excites its peristalsis,

and even carnivorous animals may suffer seriously from constipation if fed solely on such easily absorbable material as milk, eggs, and meat. A certain number of men place themselves on just such a diet. Though their intestines possess a normal irritability, the stimulus to peristalsis is lacking and they suffer from constipation. If they take foods which stimulate the intestines either by reason of their coarse, indigestible character, or by reason of their content of chemical irritants, such as the organic acids, then the constipation is cured. A lack of water in the chyme may lead to constipation. This is probably the cause of the constipation which so frequently accompanies dilatation of the stomach, with hypersecretion and the vomiting of large quantities of fluid. Profuse sweating also frequently leads to constipation, probably because it increases the absorption of water from the intestinal contents.

(*b*) *Lessened Intestinal Irritability.*—In other cases of constipation the normal irritability of the intestines is reduced more or less, and consequently the normal stimuli are not followed by the customary response. This is apparently the cause of the constipation which sometimes accompanies chronic catarrh and atrophy of the mucous membrane of the large intestines.

(*c*) *Muscular Weakness.*—It is evident that no irritation will prove of any value when the muscular coat of the intestine is greatly weakened by muscular paralysis or atrophy.[124] Such a muscular atrophy may or may not be associated with atrophy of the mucous membrane. Peritonitis is frequently accompanied by constipation, and even by total paralysis of the intestines. The exact relation between the two is not very clear, but, in some cases at least, the inflammatory process has extended from the peritoneal covering of the bowel into the muscularis.

(*d*) *Nervous Causes.*—The pathological significance of

[124] Nothnagel, Ztft. f. klin. Med., vol. iv. 422.

the ganglia within the intestinal wall and of their nervous connections is quite unknown. Degeneration of this nervous apparatus has been described in cases of lead poisoning and of chronic constipation,[125] yet similar changes have been observed in other conditions.[126]

Constipation may be associated with diseases of the central nervous system, such as neurasthenia, melancholia, and many organic changes. The cause of this constipation is not always clear. Occasionally it is of the spastic type, which will be described below. Possibly in some cases the central structures directly inhibit the intestinal movements through the splanchnic nerves, or possibly there is a diminution in the normal nervous influences, which tend to increase peristalsis. Both of these, however, are pure hypotheses.

Thus we see that many causes may lead to constipation. Improper food, reduced irritability of the intestines, weakness of the intestinal musculature, abnormal nervous influences,— all may act independently or in combination. Some cases of constipation are cured by exercise, although we do not know how it is effected.

The act of defecation is often assisted by the contractions of the abdominal muscles, although in the perfectly healthy man this is not necessary, and the peristalsis of the large intestines suffices to empty them. In most cases of constipation the intestinal peristalsis is primarily at fault, and it is rare to find the rectum filled with unexpelled fæces. If such be the case, however, then either the presence of the fæces in this locality fails to produce the normal stimulus to defecation, or the abdominal muscles do not furnish the help which may be necessary to expel the accumulated material.

[125] Jürgens, Berl. klin. Wochenschr., 1882, p. 357; Maier, Virch. Arch., vol. xc.

[126] Sasaki, Virch. Arch., vol. xcvi. p. 287; Schleimpflug, Ztft. f. klin. Med., vol. ix. pp. 52, 152.

(*e*) *Spastic Constipation.*—Finally, there is a form of constipation which is due to a tonic spasm of the smooth muscle of the intestines.[127] Such a spasm may be produced by the action of lead and by meningitis, and the condition may also occur in association with neurasthenia and hypochondriacal conditions. In spastic constipation, certain portions of the intestines, especially of the colon, are firmly contracted, and do not propel the chyme. These contracted intestines may sometimes be felt through the abdominal wall as round, hard, somewhat sensitive cords. The spasm of the intestines often causes colic, and the fæces are often hard and of small caliber, which configuration results from the spasm of the intestines. The treatment of this form of constipation should be directed to the relief of the muscular spasm.

Effects of Constipation.—The effects of constipation are for the most part subjective, and the general nutrition of the patient rarely suffers. Defecation is often extremely difficult, and the worry about this tends to upset the nervous equilibrium of the patient. Immediately after defecation he feels brighter and his head feels freer. These sensations are partly suggestive, but are certainly not wholly so, although their cause has not been satisfactorily explained.

(Constipation is often associated with an excess of ethereal sulphates in the urine,[128] indicating excessive intestinal putrefaction, and it is possible that these putrefactive products may cause some of the general symptoms of constipation. It is interesting to note, however, that fewer bacteria are passed in the fæces during constipation than during health.[129]—Ed.)

Intestinal Obstruction.—The lumen of the intestines may be obstructed by causes that lie outside of it and compress or kink the tube. A long mesentery and peritoneal adhesions

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[127] Fleiner, Berl. klin. Wochenschr., 1893, No. 3.

[128] Herter, Lectures on Chem. Path., p. 204.

[129] Strasburger, Ztft. f. klin. Med., vol. xlix., Nos. 5 and 6.

will favor kinking. On the other hand, the cause of the obstruction may be situated within the intestines. Tumors or scars of the wall, large gall-stones or fecal stones, or even masses of hard fæces may practically occlude the canal. A paralysis of a piece of intestine, from whatever cause, will produce the same effects as an obstruction, for the chyme collects and decomposes in this paretic portion, and the comparatively healthy muscle above is frequently unable to force it by.

Movable intestines may readily slip into openings, formed either by outpocketings of the peritoneum or by fibrous bands left from earlier inflammations. A hernia is produced by the entrance of a viscus, especially of intestines or omentum, into a sac of peritoneum that does not contain these structures normally. In some instances the sac itself is physiological, as is the case with the fossa duodenojejunalis and the lesser peritoneal cavity; in others, the sac is pathological, as is the case in inguinal and femoral hernias.

The viscera are usually forced into the sac by an increased intra-abdominal pressure, such as may be caused by coughing, defecation, or muscular effort. The intestines lying within the sac may functionate normally and give rise to no serious symptoms. On the other hand, the passage through them may become obstructed. The entrance to the hernial sac is usually comparatively narrow, and if the pressure upon the veins at the mouth of the sac be sufficient to interfere with the return flow of blood, then œdema develops, the volume of the intestines increases, and their lumen may be closed, usually at the narrow neck of the sac. The mechanism that leads to the obstruction in such cases is thus easily understood. It is often extremely difficult to return the œdematous loop of intestines into the abdominal cavity, partly because it is not easy to apply a pressure upon them equal to that which forced them out, and partly because the intestines have become greatly swollen from the œdema.

No adequate explanation has yet been given for the sudden obstruction that sometimes develops in hernias which have existed for a long time without producing symptoms. Experiments on the cadaver have, indeed, demonstrated that when the intestinal coils are overfilled it is difficult to empty them, for they tend to become kinked, and the mucous membrane often slides over the muscularis, so that it lies in folds at the neck of the sac. Yet these experiments do not explain why, at a particular time, the intestines should become overfilled; and, furthermore, the neck of the sac may not be especially narrow in these chronic cases. It seems to me that insufficient attention has been paid to the possibility that there may be a primary paralysis of the muscularis in these cases, which would allow the intestinal contents to accumulate at one spot. This hypothesis may possibly serve to explain many cases in which no mechanical cause can be found for the obstruction. The question cannot be finally answered, however, until we possess more evidence from clinical and experimental sources.

If a piece of intestine possesses a long mesentery with a short attachment to the posterior abdominal wall, as is the case, for example, with the sigmoid flexure, then it is liable to become twisted about its pedicle, thus producing the condition known as volvulus. The rapid distention with gas, that follows the volvulus, interferes with the movements of the intestines, and prevents them from untwisting, and the lumen of the canal is obliterated at the point of twisting.

Intestinal obstruction may finally result if a portion of the intestines is carried downward toward the anus within the portion immediately succeeding it. The cause of such an intussusception is somewhat obscure.[180] It cannot be reproduced experimentally by the mere paralysis of an intestinal loop. It would rather appear as if one portion of intestines

[180] Nothnagel, Darmkrankheiten; Nothnagel, Ztft. f. klin. Med., vol. iv. p. 555; Leubuscher, Virch. Arch., vol. lxxxv. p. 83.

drew itself over another that was tetanically contracted, and that the invagination increased by the successive inclusion of freshly contracted portions. A similar process is frequently seen in the normal intestine, but the invagination is then neither extensive nor permanent. We do not know what interferes with a straightening out of the canal in the pathological cases. When the invagination has once passed beyond a certain limit the circulation of the enclosed intestines is interfered with, and oedema follows.

In all these obstructions the symptoms depend mainly upon the degree of stenosis and the rapidity with which it develops. If the lumen of the bowel is only partially and gradually encroached upon, the intestines lying immediately above the obstruction contract more forcibly than usual and their muscular tissue undergoes hypertrophy.[131] The cause of these increased contractions is not very certain.[132] Gases frequently collect above an experimental stenosis, and these, by distending the walls of the intestines, would increase the peristaltic movements. Yet it often happens that no abnormal collection of gases can be demonstrated even though the peristalsis is increased and the muscle hypertrophied. A moderate stenosis may last for months without giving rise to any symptoms other than slight constipation whenever the food is not properly chosen.

If the lumen of the bowel is totally occluded, the resulting symptoms are entirely different from those of a gradual and partial obstruction. A total occlusion may develop acutely, or it may come on during the course of a chronic obstruction, owing to the inability of the muscle to force material past the partial stenosis. In either case the intestinal contents stagnate above the point of obstruction. The bacteria then multiply rapidly, for their growth is no longer held in check by the

[131] Herczel, Ztft. f. klin. Med., vol. xi. p. 221.
[132] Nothnagel, Ztft. f. klin. Med., vol. iv. p. 532.

onward movement of the chyme. The resulting decomposi-
tions are of various kinds, depending partly upon the bacteria
present and partly upon the material subjected to their action.
When the obstruction affects the lower part of the small intes-
tines, large quantities of unabsorbed food material are stag-
nated and putrefaction is very marked; whereas, if the large
intestines are affected, some time may pass before any abnormal
decomposition is apparent, because most of the nourishment
has already been extracted from the chyme. When putrefac-
tion occurs, all its varied products are formed, and often in
large amounts. Of these, the aromatic compounds, such as
indol and phenol, combine in the body with sulphuric acid
to form the comparatively harmless ethereal sulphates. As
a result there is often a most marked increase in the quantity of
indican and of ethereal sulphates of the urine (see p. 289). It
is possible, however, that some of the poisonous compounds
resulting from the intestinal decomposition may escape neutral-
ization, and that they are responsible for many of the general
symptoms of intestinal obstruction. For example, the com-
plicating nephritis is possibly of such a toxic origin.

The most frequent symptom of intestinal obstruction is
obstinate constipation. Yet in certain forms of obstruction,
especially in intussusception, there may be diarrhœal dis-
charges, composed not of fæces, but of inflammatory or secre-
tory products of the mucous membrane at and below the
obstruction.

As a rule, however, the portion of the intestines below the
obstruction is totally paralyzed, and not even flatus escapes
through the anus. Gases collect above the obstruction and
gradually back up in the direction of the stomach. The intes-
tines which are thus distended contract vigorously, peristaltic
and tetanic contractions alternating with each other. These
can be frequently observed through the abdominal wall, espe-
cially if the obstruction is an old one and the muscularis has

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had time to hypertrophy. These muscular contractions, especially the tonic ones, frequently give rise to the most violent colic. The patient begins to vomit soon after the obstruction sets in. At first, the vomitus consists merely of the gastric contents mixed with bile-stained material from the duodenum. If the vomiting continues, however, thin, greenish-yellow material, of a fecal odor, may appear.[133] This material undoubtedly comes from the intestines, and is composed in part of unabsorbed, decomposed material, and in part of the products of intestinal secretion.

The mechanism by which this material reached the stomach is not perfectly clear. One's first thought would be that anti-peristaltic movements play an important part, for these occur in other conditions,[134] and, even though they have not been directly observed in intestinal obstruction, no reason exists *a priori* why they should not be present. Yet some deny their existence, holding that the material reaches the stomach by a sort of overflow from the intestines, which is assisted by the normal peristaltic movements.[135]

As the obstruction continues, the patient loses in weight and strength rapidly. The period of increased peristalsis is later followed by one of paralysis of the intestines. At first this cessation of intestinal movements is caused merely by the overdistention of the intestines; for it has been shown, experimentally, that greatly distended intestines cease to contract, but that they will begin to do so again as soon as the tension is diminished. In the later stages of obstruction, however, the intestinal paralysis is absolute; and, experimentally at least, no movements can be elicited. This entire absence of peristaltic movements in intestinal obstruction indicates an exceedingly

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[133] See Leichtenstern, Kongr. f. in. Med., 1889, p. 56, etc.

[134] Grützner, Deut. med. Wochenschr., 1894, No. 48; Hernmehr, Arch. f. Verdauungskr., vol. viii. p. 59.

[135] See Nothnagel, Darmkrankheiten.

grave condition, and, if help is not forthcoming, the patient dies in collapse.

Though it is generally agreed that a period of increased peristalsis always precedes the period of paralysis in chronic obstruction, some consider that this primary period is absent in some cases of acute obstruction. Yet it seems to me that a primary period of increased peristalsis is present even in these cases, but that it is of such short duration that it is often overlooked. How quickly the one follows the other depends upon the relation which exists between the degree of obstruction and the strength of the muscle. The physician who has not observed the case from the beginning might be inclined to doubt that any period of increased peristalsis has been present.

Strangulation.—The severity of the symptoms varies greatly in different cases of obstruction. In some, the meteorism, fecal vomiting, and collapse do not occur for days, whereas in others these symptoms develop within a few hours after the obstruction takes place. These variations depend largely upon the nature of the occlusion. A simple closure of the lumen of the intestines is much less dangerous than a so-called strangulation, which may accompany any of the different forms of intestinal obstruction.[136] In this latter condition the blood-supply of the intestines is affected. The mesenteric and intestinal veins are pressed upon and occluded, the arteries continue to send blood into the intestines, and œdema results. These vascular changes, together with injuries to the nerves of the peritoneum, are apparently responsible for the rapid and alarming symptoms which ensue. The walls of the intestines become infiltrated with fluid, and bacterial decomposition proceeds with excessive rapidity within the lumen of the strangulated gut. The products of this bacterial

[136] Kirstein, Deut. med. Wochenschr., 1889, No. 49; Reichel, Deut. Ztft. f. Chir., vol. xxxv. p. 495; v. Mikulicz, Therapie der Gegenwart, 1900.

activity injure the intestinal walls, so that they no longer oppose the normal resistance to the gases which are formed. Consequently the strangulated piece of intestines becomes enormously distended (local meteorism). The violent peristaltic movements produce the most intense pain, and vomiting becomes uncontrollable. Added to these are certain general symptoms, such as the general circulatory changes, the collapse, and the rapid loss of strength. The circulatory disturbances are caused, in the first place, by reflexes from the peritoneum that act upon the heart and vessels, but especially by those that influence the splanchnic vascular area. In the second place, they are probably produced directly by the toxic action of putrefactive products absorbed from the intestines.

Meteorism.—The intestines of healthy individuals contain gases composed in part of swallowed air and in part of those which arise from the decomposition of the intestinal contents by the digestive juices, and especially by bacteria. When air is swallowed, the oxygen in it is absorbed quite rapidly, so that the small intestines rarely contain this gas. The nitrogen, however, remains in the canal for a much longer time. Carbon dioxide is set free by the action of acids upon the carbonates in pancreatic juice, bile, and succus entericus, but it is generated in much larger quantities during carbohydrate fermentation. The latter also yields hydrogen and marsh gas, and the putrefaction of proteids produces small quantities of hydrogen sulphide. Of these various gases, the carbon dioxide is absorbed by the blood quite readily, whereas the nitrogen, methane, and hydrogen are absorbed much more slowly. The quantity and quality of the intestinal gases vary greatly, even in a healthy man; for they depend largely upon the quality and quantity of the food taken and upon the varieties of bacteria that happen to be present.

These intestinal gases may produce some variation in the size of the abdomen, but rarely does great distention result,

for the normal intestines can to a certain extent dispose of the gases they contain, either by absorption or by expulsion through the anus; both processes depending largely upon the tonus of the smooth muscle.

In gastro-intestinal diseases much larger quantities of gas may be formed, and those produced in greatest abundance are usually the very ones which are least easily absorbed,—viz., methane and hydrogen. Yet a mere increased production of gas does not necessarily cause meteorism either in a healthy individual, or even in some patients with intestinal obstruction. It would appear that diminished muscular tonus and insufficient absorptive capacity are of much greater importance in the production of tympanites than is an excessive formation of gases. For this reason, meteorism is especially marked in peritonitis and acute strangulation. If the intestines once yield to the pressure of gas within them, a vicious circle is established, for this very distention embarrasses their circulation, and so diminishes their ability to absorb gas.

Meteorism, therefore, tends to develop whenever a weakness of the intestinal musculature is associated with an overproduction of gas within the intestines. The milder forms of tympanites are seen in connection with dyspepsias, enteritides, and typhoid fever; the more severe in association with peritonitis and intestinal obstruction.

The meteorism that is present at times in hysterical patients has not been satisfactorily explained, but seems to depend in part upon transitory paralyses of the muscle and in part upon the swallowing of large amounts of air. Hysterical paralyses are common enough in other parts of the body, and we see no reason why they should not occur in the intestines, and the fact seems well established that many hysterical individuals swallow air in considerable quantities.

The gases from the intestines may escape into the peritoneal cavity through a perforation, and so distend it. This

is usually fatal, on account of the associated infection of the peritoneum.[187] Yet even ordinary tympanites may be exceedingly serious. The diaphragm is forced upward and its movements are restricted, the capacity of the lungs is reduced, and the right ventricle is pressed upon. In many diseases, especially in pneumonia, tympanites is a most serious complication.

Abnormal Intestinal Sensations.—These are various. In the first place, a distention of the intestines will reduce the sensation of fulness in the abdomen, and if the distention be marked, dyspnœa may be produced by the high position of the diaphragm.

Colic results from violent contractions of the intestines. It has been said that colic is never produced by the normal progressive peristaltic movements, but only by tetanic spasms. These are liable to occur whenever the stimuli for peristaltic movements are especially strong. The most severe forms of colic are seen in connection with intestinal obstruction and lead poisoning. Less severe is the colic which may accompany intestinal catarrh and cholera nostra. The pain of colic has been located by some in the muscles, in which case it would be analogous to the pain caused by cramps in voluntary muscles. By others it has been located in the peritoneum, for we know that, like the other serous membranes, the peritoneum is an exceedingly sensitive structure and inflammations in it are always accompanied by severe pain. On the whole, it seems to me more probable that the pain of colic procedes from the sensory nerves situated in the muscularis of the intestines.

Yet other pains are unquestionably to be referred to the peritoneum, such as, for example, those which accompany peritoneal adhesions. These adhesions, which, as a rule, follow some previous inflammation, often cause the most annoying pain, which becomes worse when the bands are dragged

[187] Heineke, Arch. f. klin. Med., vol. lxix. p. 429.

upon.[188] The pains of peritoneal adhesions are of the greatest practical importance, for they may harass the patient for years after the original disease has passed away.

Somewhat similar pains are often experienced by nervous individuals, and seem to be of a neuralgic nature, for no anatomical basis can be discovered for them. They will be discussed therefore in connection with diseases of the nervous system.

Diseases of the anal orifice are often the source of severe pain. Each time that hard fæces pass over the inflamed or ulcerated mucosa the most intense agony is experienced. Perhaps even more unpleasant is the condition known as tenesmus, in which a constant, violent desire to defecate harasses the patient. This is especially liable to be present in diseases of the rectum. The inflammatory changes of dysentery frequently cause this constant desire to defecate, but, owing to the lack of fecal material in the rectum, nothing except inflammatory products are passed and these with most excruciating pain.

[188] Riedel, Arch. f. klin. Chir., vol. xlvii. p. 153; Vogel, Deut. Ztft. Chir., vol. lxiii. p. 296.

CHAPTER VII.

NUTRITION AND METABOLISM.

THE activities of the living cells are associated with chemical changes within them, and with an interchange of food and waste material with their surroundings. The sum of all these processes is termed metabolism. A discussion of nutrition and metabolism ought properly to deal with each organ individually, for it is obvious that different tissues require different food materials and give rise to different waste products. Indeed, the various organs are more or less interdependent upon one another, and one organ, for example, may use material that has been elaborated by another, or may transform waste products derived from another. In our present state of knowledge, however, it is impossible to discuss metabolism from the stand-point of the individual organs, and we are obliged to consider the metabolic processes that take place in the body as a whole. Our knowledge of these processes is derived mainly from examinations of the food ingested and of the various waste products eliminated.

THE QUANTITATIVE VARIATIONS IN THE METABOLISM OF FATS AND PROTEIDS.

In order to maintain the body, it is necessary to supply it with water, mineral salts, and organic bodies, which latter include the proteids, carbohydrates, and fats. It is not altogether certain, however, that this enumeration fully expresses the needs of the body, for there have been failures to maintain animals upon a diet consisting solely of casein, sugar, fat, and salts.[1]

The Caloric Needs of the Body.—The food ingested is

[1] Lumin, Ztft. f. physiol. Chem., vol. v. p. 31.

utilized partly to repair the tissue waste, and partly to furnish energy for muscular movements and for bodily heat. For these last purposes it is practically immaterial in what form the energy is provided, whether it be as carbohydrates, fats, or proteids; the essential point being that the quantity of food is sufficient. (The energy contained in the various food-stuffs is transformed by the body into mechanical work, chemical work, and, especially, into heat. Indeed, Rubner has shown that almost the entire energy of the food leaves the resting body in the form of heat, and that the heat which results from combustion in the body is the same as that which would be produced were the foods burned outside to the same waste products.

The unit for measuring quantities of heat is the large calorie, which represents the amount of heat necessary to raise the temperature of a kilogram of water one centigrade degree. When equal weights of different food-stuffs are burned in the body, different quantities of heat are liberated. Thus each gram of fat produces about 9.3 calories, each gram of carbohydrates about 4.1 calories, and each gram of proteids about 4.1 calories. It will be seen from these figures that the energy derived from fat is relatively greater than that derived from carbohydrates or proteids. Indeed, one gram of fat furnishes about the same energy as does 2.3 grams of either of the other two. It is possible, with certain limitations, to replace any constituent of the diet by any other, without disturbing the equilibrium of metabolism, providing due attention be paid to the caloric value of each food-stuff. Each gram of fat in the food, for example, may be replaced by 2.3 grams of carbohydrates, etc. It is furthermore possible to calculate the total quantity of energy contained in any particular diet and in this manner to estimate whether or not this diet contains a sufficient amount of energy to cover the caloric needs of the individual.

The amount of energy that must be supplied to the body depends primarily upon the activities of the tissues, and it is subject to many influences. This amount has been estimated empirically from the mean quantity of food taken by different individuals. For an adult of average nutrition and size, the following have been given as the approximate number of calories necessary per kilo of body weight:[2]

	Calories.
Resting in bed	30 to 34
Quiet, out of bed	34 to 40
Moderate work	40 to 45
Hard work	45 to 60

A small person needs a relatively greater supply of energy per kilo of weight; for, as is well known, a small body has a relatively large surface, and would consequently lose more heat in comparison to its weight. This is one reason why children need more food than adults in proportion to their weight. On the other hand, stout individuals need relatively less food; and instead of the normal thirty-four to forty-five calories, they need only about twenty-six to thirty-six calories per kilo of body weight. This difference is due to the facts that a large body has a relatively small surface; that the thick layer of fat protects these persons from heat losses; that the fat itself is practically dead tissue in the body, and does not consume energy; and, finally, that stout individuals usually take a minimal amount of exercise.—ED.)

Not all variations in the caloric needs of different individuals are thus easily explained, and there are reasons for assuming that the cells of different persons manifest different needs for energy. At least, no other satisfactory explanation can be given for the fact that certain men seem to require very much smaller quantities of proteids and of energy than do others.[8]

[2] Moritz, Gründzuge der Krankenernährung, p. 248.
[8] Buys, cit. in Jahresber. f. Tierch., vol. xxiii. p. 491.

The Proteid Needs of the Body.—The food must furnish the body not only with a sufficient amount of energy, but also with a certain minimum of proteids, which is utilized in part in the repair of the waste within the cells.

The steps whereby the proteids of the food are prepared for use in the body are not yet accurately understood. It was formerly believed that these substances were altered very little before being used, but more recent work would indicate that the proteids, taken as food, undergo extensive cleavage in the body, and that the products of such cleavage are again synthesized into compounds more suitable for use in the cells.[4] It is known, for example, that unusual proteids, taken by mouth, cannot be demonstrated afterwards in the portal or systemic blood, that life may be maintained even though only a single proteid be taken in the food, and that, finally, if two different species of animal receive the same food, the proteids of their bodies still remain distinguishable (see p. 171). On the other hand, no success has attended the efforts to maintain a nitrogenous equilibrium by replacing the proteids of the food with cleavage products of a simpler composition than are the albumoses and peptones. It would appear from this as if the body is unable to build up the proteid molecule unless certain substances, not at present known to us, are furnished to it, or that it can utilize the products of proteid cleavage only when they are supplied in the nascent condition. It is possible, however, that the cleavage products have never yet been given in proper proportions, and that we shall yet be able to maintain life without using proteids.[5]

The mimimal amount of proteid, necessary for the needs of the body varies with the condition of proteid nutrition that is to be maintained and with the work which the body per-

[4] Loewi, Arch f. exp. Path., vol. xlviii. p 303; Cohnheim, Ztft. f phys. Chem., vol. xxxiii. p. 9.

[5] Leowi, loc. cit.

forms.[6] Although the quantity given by Voit seems considerable (one hundred and eighteen grams of proteid for a man of seventy kilograms), and although less is sufficient for an individual when he is at rest or when other forms of food are taken in great abundance,[7] nevertheless there is a growing inclination to regard these older figures as approximately correct for a healthy individual, and to believe that the capabilities of the body are liable to be diminished if less than this amount of proteid food be taken. On the other hand, as Rubner has shown, proteids in the food should not exceed a certain maximum proportion, for if they do, an excessive amount of heat is liberated immediately after meals, and this is not only useless but may be directly harmful if the heat regulation in the body be imperfect (see p. 322).

In what way the cells are supplied with proteids is not known, though it would seem probable that they derive them from the blood plasma. This supposition is supported by the results of precipitin experiments, for these have shown that the proteids of the plasma and of the cells of an animal are apparently more closely related than are the proteids from the same organs of different species of animals.

We do not know what regulates the needs of the cells for proteids, though many facts would seem to indicate that only a small part of the minimum proteids necessary for the body actually becomes living protoplasm. It is possible that the excess is necessary for the reason that only a certain portion of the proteid molecules of the food can be utilized in building up living tissue.

Inanition.—Inanition may be due to a variety of causes. Of these, the most important are, first, an insufficient inges-

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[6] Erwin Voit and Korkunoff, Ztft. f. Biol., vol. xxxii. p. 58; J. Munk, Du Bois' Arch., 1896, p. 183; Rubner, Energieverbrauch.

[7] See v. Noorden, Path. d. Stoffwech., p. 114; Rubner, Ztft. f. Biol., vol. xix. p. 313.

tion of food, either from lack of food or lack of appetite, and secondly, an insufficient absorption of material from the gastro-intestinal canal. Practically, inanition is most frequently seen in connection with diseases of the digestive system.

It is necessary to distinguish an insufficient supply of food as a whole, a caloric insufficiency, from an insufficient supply of proteid material, a proteid insufficiency. These two are more or less independent of each other, and it is possible, for example, that a patient should gain in weight and yet suffer from an insufficiency of proteids.

If too little food be supplied to the body, then the individual must live upon his own tissues. His glycogen and fats can furnish him with energy. In addition to this, however, he consumes a certain minimal quantity of proteids, which are derived from the less important organs of his body. The amount of proteids thus consumed depends partly upon the quantity of fat and glycogen at his disposal and partly upon individual peculiarities. During the first few days of an absolute fast the excretion of nitrogen is influenced by the quantity of proteids that had been taken just before the fast began. As soon as this excess of nitrogen has been elimi-nated, however, the quantity in the urine sinks to a minimum and remains there for a few days. Later it again increases possibly because all of the glycogen in the body has been used up.[8]

During the earlier stages of starvation, therefore, the energy necessary for muscular movements and for heat, is supplied by the combustion of the glycogen and fats stored up in the body. The more valuable proteid material is thus protected from consumption. When the store of non-nitro-genous material comes to an end, however, the proteids them-selves must be utilized to supply the necessary energy to the

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[8] May, Ztft. f. Biol., vol. xxx. p. 29; Lehmann, Müller, Munk, Senator, Zuntz, Virch. Arch., vol. cxxxi. Supplement.

body.[9] The living tissues then break down rapidly; yet a certain discrimination still takes place. The more important organs live at the expense of the less important ones, and Voit has shown that the former will retain their normal weight practically unaltered up to the end. The greatest loss is sustained by the muscles and fatty tissues; then follow the skin, the liver, and the bones; whereas the heart and central nervous system are spared to the very last.[10]

(During acute starvation the elimination of chlorides in the urine is markedly diminished and may reach one tenth or less of the normal amount. This is due to the tendency on the part of the kidneys to maintain a constant quantity of chlorides in the body; and when none are taken in the food, the small amount eliminated corresponds approximately to that derived from the breaking down of the tissues. In the later stages of starvation the excretion of calcium and magnesium salts, as well as of the phosphates, is increased; probably because there is a pathological breaking down of the osseous tissues.—Ed.)

Absolute starvation is rarely seen by the physician, but partial inanition is by no means infrequent, and its treatment furnishes one of the most important problems that confront the practitioner. Usually, in these cases, both the total caloric energy and the proteids in the diet are insufficient. The amount of this deficiency may vary up to absolute starvation.

The effects of starvation upon the individual depend, in the first place, upon how complete it is. If the body consumes thirty-five calories per kilo a day and if it receives only ten from the food, then it must supply twenty-five calories from its own substance, and the condition is naturally a much more

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[9] E. Voit, Ztft. f. Biol., vol. xli. p. 550; Schulz, Pflüger's Arch., vol. lxxvi. p. 379; ibid, Münch. med. Wochens., 1899, No. 16.

[10] C. Voit, Physiologie d. Stoffwechsels., p. 95; Sedmayer, Ztft. f. Biol., vol. xxxvii. p. 35.

serious one than if it had received thirty calories in the food and had supplied only five from its own substance. Furthermore, starvation is withstood much better if the patient be stout, for he then has a larger amount of fat that can be utilized to supply energy. This serves to postpone the time at which the non-nitrogenous stores in the body give out, and the living tissue itself must be consumed to supply energy. Finally, the course of inanition is influenced by the demands made upon the energy within the body, and the condition is a more serious one when the individual must work or when he is not well protected by clothing, etc., from losses of heat.

In certain diseases, hunger and insufficient nourishment are often surprisingly well borne; better, indeed, than they are in health, for the body then seems to be able to limit its consumption of proteids and energy. Astonishingly low figures have been found in such cases, and patients have often gained in weight on a diet that would be entirely insufficient for a healthy man.[11] The amount of heat produced in the body during a short fast is about the same as that produced when the individual is consuming moderate amounts of food. If, however, the patient suffers from prolonged partial starvation, then the amount of heat produced in the body seems to be lessened, and one gets the impression that the ability to limit the expenditure of energy is quite characteristic of wasting diseases, such as diabetes, for example.

The Effects of an Oversupply of Food.—It is necessary to discuss the effects of increasing the nitrogenous and the non-nitrogenous elements in the food separately, for the laws governing each are different. We may say, in a general sort of way, that the cells of the body ordinarily decompose all the proteids taken in the food. When proteids are taken in

[11] F. Müller, Ztft. f. klin. Med., vol. xvi. p. 496; Nebelthau, Ztrbl. f. in. Med., 1897, p. 977; G. Klemperer, Ztft. f. klin. Med., vol. xvi. p. 550; Richter, Arch. f. exp. Path., vol. xliv. p. 239.

abundance, and the total caloric energy of the food is not too greatly increased, there is merely a slight retention of nitrogenous material during the first few days of the new diet. Very soon, however, the body reaches a condition in which it is consuming all the proteids furnished to it, and it is then said to be in nitrogenous equilibrium.

If the tissues happen to be in need of new material, as is the case during growth and convalescence, then it is possible that a considerable proportion of the extra supply of proteids may be retained in the body and may be built up into living tissue.

It is even possible to cause a considerable retention of nitrogenous material in the bodies of normal animals by feeding them with large quantities of both nitrogenous and non-nitrogenous food.[12] Apparently the same result may be attained even more easily in man.[13] We do not know certainly whether this nitrogenous material is retained in the body as proteids or as other compounds. It is interesting to note in this connection that when growing children or convalescents retain nitrogenous material in their bodies, they are taking a diet that contains an excessive amount of energy.[14]

The mere ingestion of fats or carbohydrates in great excess tends to diminish the excretion of nitrogen in the urine; or, in other words, it tends to cause a retention of nitrogenous material in the body. This fact has been variously interpreted. E. Voit considers that the cells utilize those foods which are supplied to them in greatest abundance; whereas Pflüger and others believe that the selection of material for consumption is a property of the living protoplasm, and as

[12] Pflüger, Pflüger's Arch., vol. lxxvii. p. 424.

[13] Lüthje, Ztft. f. klin. Med., vol. xliv. p. 22; Kaufmann and Mohr, Berl. klin. Wochens., 1903, No. 8; Kaufmann, Ztft. f. diät. Ther., vol. vii., Nos. 7 and 8.

[14] Camerer, Ztft. f. Biol., vol. xxxiii. p. 320; Heubner, Ztft. f. diät. Ther., vol. v. p. 1; Svenson, Ztft. f. klin. Med., vol. xliii. p. 86.

such is almost independent of which foods are supplied in excess. We cannot enter into a discussion of this physiological problem, but may state our belief that the growth of living tissue depends primarily upon the activities of the cells In virtue of some unknown property these latter grow and multiply, and their growth and multiplication are especially excited by functional activity; providing, of course, that a supply of building material is at hand. When the physician wishes to increase the living protoplasm of the body, therefore, he should remember that it is more important to increase the functional activities of the cells than to furnish the body with an oversupply of food.

In the metabolic cleavage of proteids certain non-nitrogenous compounds are split off, related in all probability to the carbohydrates. The laws, governing the consumption of these, are the same as those governing the consumption of other non-nitrogenous substances.

We have seen that the amount of energy needed by the body depends primarily upon the work performed and the heat expended. A person lying in a warm bed, for example, expends less energy than does one who works hard eight or ten hours each day, or who is exposed to very cold weather. When excessive quantities of non-nitrogenous food are taken in the diet, the excess is not burned up, as are proteids, but it is stored in the body, as glycogen or as fat. A discussion of the storage of glycogen will be postponed until we consider the subjects of diabetes and of fever. In regard to the storage of fats, it must be remembered that this is largely independent of the nitrogenous metabolism, and that it is possible for the body to lose nitrogen and at the same time to gain fat, and that it is even possible for death to occur from lack of proteids at a time when the fat of the body is well preserved.

(Rubner [15] has shown that if dogs be kept at a uniform

[15] Die Gesetze des Energieverbrauchs bei der Ernährung, 1902.

temperature of 33° C., the ingestion of any food is followed by an increased production of heat in their bodies. The amount of this excessive quantity of heat varies according to the character of the food. When proteids are taken, about thirty per cent. of the energy contained in them was immediately given off as extra heat; when fats were taken, about twelve per cent. was thus eliminated; and when carbohydrates were taken, about six per cent. This specific action of different foods remains the same whether small, medium, or large quantities are ingested. If the animals were exposed to a low temperature, the extra heat thus produced was utilized to keep their bodies warm, thereby avoiding the necessity of increasing the ordinary production of heat in the muscles. At a temperature of 33° C., however, the extra heat was eliminated without apparently serving any useful purpose.

It seems improbable that the increased production of heat which follows the ingestion of proteids could be caused by the increased activities of the digestive glands; for meat extracts stimulate these glands, and yet do not increase the heat production in the body. Rubner believes that this excessive heat is caused by a cleavage of the proteid molecules into their nitrogenous and non-nitrogenous constituents. He supports this view with observations on the effect of artificially increasing the proteid metabolism by the administration of phloridzin, and he shows that the heat so produced was approximately the same as when proteids were taken by the mouth.—Ed.)

Disturbances in Fat Metabolism.—We have said that, if large quantities of non-nitrogenous material are taken in the food, the unused excess is stored up in the body either as glycogen or as fat. The quantity of fat in the body depends, therefore, to a great extent upon the relation that exists between the supply of, and the demand for, energy-producing material.

Different classes of food stuffs produce different effects as regards the tendency to accumulate fat. For example, when proteids are eaten, the general metabolism is accelerated far more than when fats or carbohydrates are taken, and consequently less energy is left for storage. Whether fat is ever formed directly from proteids or not, need not be discussed here, for very little, if any, is derived from this source. In either case, an excess of proteid material in the food would favor a retention of fat in the body, for the reason that the non-nitrogenous products of proteid cleavage may be utilized for energy. This would spare the fats and carbohydrates, and allow them to be stored.

The carbohydrates of the diet that are not burned immediately are deposited in the body partly as glycogen and partly as fat.[16] That carbohydrates may give rise to fat in the body has been demonstrated any number of times. Apparently this transformation takes place with the elimination of carbon dioxide, for the respiratory quotient may rise to as high a figure as 1.3 during this formation of fat from carbohydrates.[17] The fat that is thus formed is rich in stearin and palmitin, but poor in olein.[18] In what part of the body the transformation takes place is not known, though there is some evidence that it occurs in the liver.

If fat is ingested in excessive quantities, it is deposited as such in the body. The composition of animal fat is therefore, to a certain degree, dependent upon the composition of the fats taken by the mouth.[19] In spite of this fact, however, the body fat in man and in many animals preserves a fairly constant composition. This may be explained on the assump-

[16] For the literature and discussion of this subject, see Rosenfeld in Asher-Spiro, Ergebnisse der Physiol., vol. i. p. 345; vol. ii. p. 50.

[17] Bleibtreu, Pfluger's Arch., vol. lxxxv. p. 651.

[18] Rosenfeld, loc. cit.

[19] Ibid., p. 673.

tion that the body tends to pick certain fats out of the food for storage, or that the food commonly taken is really of a more constant composition than is ordinarily believed.

The relation of the ingestion of fluids to fat metabolism is a much-discussed and still unsettled subject. Many stout individuals drink a considerable quantity of liquids, especially of beer, and it often happens that when the latter is stricken from the diet, a loss of weight promptly follows. This result is due in part to the loss of energy that would be derived from the alcohol and carbohydrates of the beer; but it may be due in part to the lessened quantity of fluids taken. Small amounts of other drinks, such as coffee, tea, bouillon, or light wine, are often taken to increase the appetite, and if these be omitted the individual may eat less and so lose weight from this cause. Although these facts are of the greatest practical importance, they have no theoretical bearing on the question as to whether or not fluids directly influence the storage or decomposition of fats in the body. Though this question has not yet been satisfactorily settled,[20] it seems worth while to review some of the evidence bearing upon it and call attention to some of the difficulties encountered in its solution.

It is a surprising fact that while animals are being fattened, very little water is usually allowed them;[21] from which we may infer that a relatively dry diet certainly does not seriously interfere with the accumulation of fat in the body.

The question as to the effect of liquids upon the accumulation of fat in man is a difficult one to solve; for in him the only method whereby we can practically estimate a gain or loss of fat is weighing, and a difference in weight might be equally well caused by a change in the quantity of proteids, of gly-

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[20] Oertel, Allge. Ther. d. Kreislaufstor., 1891, p. 147; Lorenzen, Diss. Erlangen, 1887.

[21] Hennenberg, Kongr. f. in. Med., 1885, p. 46; Vogel, Jour. f. Landwirtsch., vol. xxxix. p. 37.

cogen, or of water in the body. The first two of these may be neglected practically, for the variations that they undergo are not great. The third, however, is of the utmost importance in a consideration of this question, and it constitutes a considerable source of error whenever we assume that a gain or loss of weight is necessarily caused by a correspondingly great gain or loss of body fat.

Stout persons ordinarily drink large quantities of water, probably because they perspire so freely, and this water is not all immediately excreted, but some is stored in the body. If, now, the patient refrains from drinking water, and takes much exercise, he loses weight rapidly. The main cause of this early loss of weight, however, is the loss of water. There simply results a drying-out of the body.[22] Indirectly this loss of water may assist in reducing the fat in the body, for when the weight of a stout person is lessened by the loss of fluids, it is possible that he will take more exercise and so consume more fat.

It will be seen from these considerations that different factors render this question a most difficult one to solve. At present we possess no conclusive evidence that the limitation of fluids directly influences fat metabolism; though such a limitation may indirectly reduce the weight of the body either by removing water from it, by diminishing the amount of food taken, or by increasing the ability to take exercise.

Pathological Accumulations of Fat. No sharp distinction can be made between pathological and physiological accumulations of fat, and it is often a matter of opinion as to whether a given person is too stout or not. The line separating the normal from the abnormal should be drawn at the point where the general health and the capabilities of the individual begin to be impaired. When these latter are

[22] Dennig, Ztft. f. phys Ther., vol. i. p. 281 ; Zuntz, Ther. d. Gegenw., 1901, July.

affected, we are justified in speaking of a pathological accumulation of fat.

Fat tends to collect in certain parts of the body, especially in the subcutaneous tissues and the mesentery, and about the heart, the kidneys, and the liver. In young animals it may also collect in the muscles between the individual muscle-fibres,[23] whereas in older animals it tends to collect in the above-mentioned situations.

The individual who suffers from excessive accumulations of fat gradually becomes less and less able to work. This is due, in part, to the increased weight of the body, for more exertion is required to execute the same movements. On this account, fat persons are inclined to avoid all unnecessary exertion. If they do so, their muscles tend to atrophy from disuse, and a vicious circle is thus established. The patient avoids movements because his body is too heavy, and the lack of exercise weakens his muscles so that he is less able to move. Most stout people also perspire very readily, because their thick layer of fat diminishes the amount of heat given off from the surface of the body by radiation and conduction. This sweating is very unpleasant, and furnishes another excuse for their avoiding exercise.

In Rubner's laboratory the capabilities of lean and stout men have been carefully studied under different conditions of temperature and humidity,[24] and it has been shown that, as the temperature and humidity of the air increases, the ability of stout people to work diminishes rapidly, for they quickly become overheated, and perspire profusely. Their fat thus renders them less able to work, and soon causes unpleasant subjective sensations from overheating.

Finally, very stout people avoid exertion because they get

[23] F. Müller, Path. d. Stoffwechsel., p. 204.

[24] Schattenfroh, Arch. f. Hyg., vol. xxxviii. p. 93; Wolpert, ibid., vol. xxxix. p. 298; Rubner, Beiträge z. Ernäh. im. Knabenalter, Berlin, 1902.

out of breath so easily. Their dyspnœa is due, in the first place, to the increase in abdominal fat, which limits the movements of the diaphragm; in the second place, it is due to the additional weight of the body, which necessitates more actual work for the accomplishment of the same movements; in the third place, it is due to a weakness of the muscles or to an associated anæmia; and finally it is due to the cardiac disturbances, which are so often present in obese individuals and which have already been described (p. 68). It is thus apparent that excessively fat persons suffer in a variety of ways, partly on account of the presence of the fat itself and partly on account of the weakness of the general or cardiac musculature.

The primary cause of obesity lies in a misproportion between the energy taken in the food and the amount expended by the body. As we have just said, stout people usually show a disinclination to exercise, and this, by diminishing the expenditure of energy, favors the deposition of new fat in the body. Furthermore, many stout persons eat to excess, and the carbohydrates and fats that they eat are especially disadvantageous. In certain instances the absorption of proteids seems to be diminished, and the patient suffers, at one and the same time, from too much fat and too little proteid.[25] Alcoholic beverages certainly tend to increase obesity. In the first place, they furnish a not considerable amount of energy in the form of alcohol, and frequently also in the form of carbohydrates (beer); and, in the second place, they tend to take away the energies of the individual, and so to diminish the exercise that he takes.

These causes, singly or together, are responsible for most cases of obesity. It is merely a problem in arithmetic. A certain amount of energy is taken in the form of food, a certain amount is lost as heat and work, and the remainder is stored up in the body, mainly as fat. As soon as the accumu-

[25] Rubner, Beitr., etc.

lation of fat begins to deter the patient from taking active exercise, a vicious circle is established, and he tends to increase in weight more and more.

The question has been raised as to whether all cases of obesity can be explained in this comparatively simple manner. Physicians certainly have the impression that not all cases are due to a simple misproportion between the energy taken in and that given out, and it seems as if many persons, in spite of abundant nourishment and little exercise, remain lean, whereas others become stout, even though they eat but little and do considerable work.

It is extremely difficult to form a judgment on this question. In the first place, it often happens that, although the patient thinks he is not eating to excess, he is really doing so. Then we have no accurate method for determining the amount of exercise that he takes. There are the most extraordinary individual variations in this respect, as can be readily imagined if we compare a nervous individual, constantly in motion and all his muscles tense, with a phlegmatic person, who never executes an unnecessary movement. The energy expended by each is vastly different, even while they are accomplishing the same task. Finally, factors that influence heat losses must be considered; such as, for example, the thickness of the clothing, the temperature of the surrounding air, its moisture, etc. All these influence, to some degree, the consumption of energy in the body.

Yet, even allowing for all of them, there still remains the impression that some men exhibit an unusual relationship between the diet, the exercise taken, and the fat deposited. Some children, for example, show a remarkable tendency to become stout; or certain families are known for the obesity of their members; some anæmic persons tend to accumulate fat, etc. To be sure, it may be answered that, when the parent eats to excess, the children learn the same habit; or that the anæmias

tend to limit the amount of exercise taken, etc. Nevertheless, the impression remains that, for some unknown cause, certain individuals possess a peculiar tendency to lay on fat.

We should not, however, trust to impressions. The question is one that can only be solved by careful and exact experiments, and up to the present these have furnished no evidence which would indicate that such a constitutional tendency to obesity, in the sense of a slower rate of metabolism, actually exists. For example, Rubner has shown that, of two brothers, one stout and the other thin, the former burned up even more fat than the latter. Others have demonstrated that stout persons consume a normal amount of oxygen and give off a normal amount of carbonic acid gas during fasting; and, although the increase in heat production that immediately follows the taking of food is said to be less in stout than in thin persons,[26] we are hardly justified from this fact alone in assuming a slower rate of metabolism in the former.

The gain in weight that so often follows castration has been cited as an example of a constitutional change leading to obesity. It is certain that many, though not all, castrated animals and men gain in weight. We may question, however, whether this gain is directly due to the loss of a hypothetical accelerating influence of the genital organs upon metabolism, or whether the gain is not indirectly due to changes in the temperament of the individual, in his appetite for food, his desire to exercise, etc. Luthje,[27] has made a careful comparative study of the nitrogenous metabolism, and a partial study of the carbon and mineral metabolisms of castrated and normal dogs over a period of more than a year, and, finally, at the end of this time, he has determined the total composition of their bodies. No differences could be found between the normal and pathological animals, and we

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[26] Jaquet and Svenson, Ztft. f. klin. Med., vol. xli. p. 376.
[27] Arch. f. exp Path., vol. xlviii. p. 184; vol. l. p 268.

must conclude from these experiments that castration does not directly affect the body metabolism. Although other observers have found certain differences by other methods,[28] nevertheless it seems to me that Lüthje's experiments are the most conclusive we have.

This much is certain, that obesity results from a failure to consume all of the nourishment taken. It is possible that a lessened rate of cellular metabolism plays an important part in certain cases, though personally I do not believe that this has yet been proved.

The association of obesity with anæmia, with gout, with arteriosclerosis, and with various forms of calculi should here be mentioned, though the exact causal relation between these is unknown to us.

Pathological Changes in the Metabolism of Proteids.— As has been described, the growing child and the convalescent from infectious diseases are alike able to retain some of the nitrogen taken in the food; whereas a normal individual under like circumstances would soon come into a condition of nitrogenous equilibrium. Even in the above instances, however, a great excess of food is usually taken.

Pathological Destruction of Proteid Material.—If, as has been said, the ingestion of proteids falls below a certain limit, or if the body has no non-nitrogenous material at its disposal and is not oversupplied with proteids in the food, then the living nitrogenous substances in the tissues must be consumed to supply the body needs. In the class of cases which we now wish to consider, however, there is a pathological consumption of the body substance, and especially of its proteids, even though an ordinary amount of food be taken. If such a patient fasts, his excretion of nitrogen is considerably

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[*] Loewy and Richter, Engelmann's Arch., 1899, Supplement; ibid., Berl. klin. Wochens., 1899, No. 50; Ztrbl. f. Physiol., 1902, No. 17; Loewy, Ztrbl. Physiol., 1902, No. 50.

greater than is that of a normal individual of like weight, etc. If an attempt be made to bring him into a condition of nitrogenous equilibrium, this is often a complete failure, for, as proteids are added to his diet, the consumption of nitrogenous material also increases, so that the output of nitrogen remains constantly somewhat greater than the intake. In certain of these cases, however, it is possible to maintain a nitrogenous equilibrium by using enormous quantities of food.

A pathological proteid destruction of this character takes place in all forms of fever, and it will be referred to again in that connection. It also occurs in many patients with carcinomata and other malignant tumors,[29] in many with tuberculosis, even though no fever is present, in severe anæmias,[30] and in certain intoxications, as from phosphorus.[31] Possibly, also, it is present in other conditions, such as scleroderma, lichen ruber, and pemphigus vegetans.[32]

In the conditions enumerated, excessive quantities of fat are also frequently consumed, for the diet is often an insufficient one, but this consumption follows the ordinary physiological laws of inanition; whereas the destruction of proteids is of a pathological character. Which cells of the body suffer most from this consumption of proteids has never been determined, though one would be inclined to believe that the loss falls upon the same organs as it does in inanition (see p. 318).

Not all patients with carcinomata, severe anæmias, or tuberculosis suffer from this increased destruction of proteids, and it would appear, therefore, that other causative factors are operative in these cases. In view of the fact that certain

[29] F. Müller, Ztft. f. klin. Med., vol. xvi p. 496; Kongr. f. in. Med., 1889, p. 396; G. Klemperer, Ztft. f. klin. Med., vol. xvi. p. 550.

[30] Rosenquist, Ztft. f. klin. Med., vol. xlix. p. 193.

[31] Fraenkel and Rohmann, Ztft. f. phys. Chem, vol. iv. p. 439.

[32] Stüve, Arch. f Derm. u Syph., vol xxxvi. p 51

poisons, such as phosphorus, may accelerate the destruction of proteid material, F. Müller has advanced the hypothesis that toxic substances are also responsible for the increased proteid destruction that accompanies certain cases of carcinoma. These toxic substances have never been isolated, yet there is every reason to believe that this explanation is a correct one. Only when this hypothetical poison is produced, does the disease lead to a destruction of proteid material. This theory is supported by the fact that in tuberculosis and carcinoma we sometimes see toxic symptoms resembling those of diabetic coma.

A pathologically increased nitrogenous metabolism is a most serious condition, for it becomes impossible to maintain the patient's nutrition, and the loss of proteids may eventually prove fatal.

The Metabolism in Exophthalmic Goitre.—Many patients suffering from this disease manifest no peculiarities as regards their metabolism; others, however, show periods of fair to good nutrition alternating with periods of emaciation. This emaciation may occur even when the appetite is considerably increased. One of F. Müller's [33] patients, for example, weighing only twenty-nine kilos (sixty-four pounds,), lost both in nitrogen and general weight, even though the diet furnished as much as sixty-eight grams of proteids per day and fifty-eight calories for each kilo of body weight. In such cases a pathological consumption of both nitrogenous and non-nitrogenous material is undoubtedly taking place in the body. As a rule, it is possible to attain a nitrogenous and caloric equilibrium in these patients by giving them very large quantities of food.[34]

It is very interesting that, in Matthes's cases, the excessive consumption of proteid material disappeared after the re-

[33] Arch. f. klin. Med., vol. li. p. 401.
[34] Scholtz, Ztrbl. f. in. Med., 1895, Nos. 43 and 44; Matthes, Kongr. f. in. Med., 1897, p. 232.

moval of a large part of the thyroid gland, thus conclusively demonstrating that the pathological thyroid function increased the consumption of nitrogenous and non-nitrogenous material in the body. Indeed, it was found that if thyroid gland were administered to these patients after their operations, the excretion of nitrogen rose to what it had been previously.

The amounts of oxygen absorbed and of carbon dioxide eliminated by patients with exophthalmic goitre are greater than the normal.[35] After the removal of the thyroid gland from rabbits, these animals show an abnormally low "respiratory interchange of gases" when fasting, and if thyroid substance be then administered to them, this interchange returns to the normal.[36] We see, therefore, that in certain patients with exophthalmic goitre there is an increased consumption not only of proteids but also of non-nitrogenous materials. In this last feature the metabolism differs from the increased proteid metabolism of carcinoma, and it is even possible that the loss of proteids in exophthalmic goitre is merely secondary to the loss of non-nitrogenous material.[37]

The administration of the thyroid gland to healthy men or animals, either by way of the digestive tract or by subcutaneous injections, increases the bodily consumption of proteids and fats.[38] In a certain proportion of cases this loss may be covered by an abundant diet. Here again it is uncertain whether the destruction of proteids is secondary to the destruction of fats or not,[39] and Scholtz,[40] for example, found that when thyroid substance was given to cretins, the fat was consumed and that the proteids were not affected.

[35] Magnus-Levy, Berl. klin. Wochens., 1895, No. 30.
[36] Maier, Diss. Würzburg, 1900.
[37] F. Müller, Kongr. f. in. Med., 1897, p. 239.
[38] Schöndorff, Pflüger's Arch., vol. lxvii. p. 395; Voit, Ztft. f. Biol., vol. xxxv. p. 116.
[39] Schöndorf and Voit, loc. cit.
[40] Kongr. f. in. Med., 1902, p. 475.

A lack of thyroid function affects the body in still other ways.[41] Thus, if the thyroid and parathyroids are removed from an animal, tremors and peculiar convulsions often develop, which resemble tetany, and yet are not identical with it,[42] and fever may also be present at times in these animals. The convulsions sometimes involve the respiratory muscles and so cause death.

If the function of the thyroid glands be gradually diminished, or if, after total extirpation, the more acute symptoms are eliminated by the administration of thyroid substance, then nutritional disturbances may develop in the skin, nails, bones, and other organs. The skin becomes thick and immobile owing to a collection of a mucin-like material in the corium, the connective tissue fibrils thicken, and the hair falls out. Weakness of the muscles and disturbances of sensation are associated with a general loss of intelligence; and if the gland be removed from growing animals, the growth may be stunted.

These symptoms closely resemble those of myxœdema and cretinism, in which diseases the thyroid gland is found to be diseased or absent. The variations in symptoms seen in these diseases are probably due to the varying intensity and character of the thyroid lesion, as well as to the age of the patient when the disease began. The changes in myxœdema and cretinism are to be attributed, therefore, to an insufficient function on the part of the thyroid gland. As proof of this we have the remarkable results obtained by the administation of thyroid substance to these patients.[43]

Exophthalmic goitre, on the other hand, is probably due to an increased thyroid function. In favor of this view are the facts that a partial extirpation of the thyroid has improved

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[41] See Ewald in the Nothnagel System.
[42] Kast, Kongr., f. in. Med., 1896, p. 161.
[43] Osler, Am. Jour. Med. Sci., vol. cxiv. p. 377.

or cured many patients with this disease, and that the administration of large quantities of thyroid substance to a normal individual will produce symptoms somewhat resembling those of exophthalmic goitre.

THE QUALITATIVE CHANGES IN METABOLISM.

Unfortunately, we know but little concerning the intermediary stages through which the various constituents of the body pass before they are finally eliminated through the excretory organs as highly oxidized products. Though it would be logical to discuss the catabolism of each substance separately, and to follow each to its excretion, this is not possible with our present limited knowledge. We shall therefore merely consider, first, certain facts concerning the proteids, and, later, certain abnormal excretory products.

The proteids taken in the food are split up in the body into nitrogenous and non-nitrogenous constituents. The former probably consist of ammonium compounds, and the greater part of these are synthesized into urea, probably in the liver, and are then eliminated through the kidneys. Nitrogen is present in the urine in various forms; about eighty-five per cent. being urea, from two to five per cent. being ammonia, and the remaining ten per cent. being made up of a variety of compounds of which uric acid and the purin bases form a large part.

Whether or not the proteid catabolism in the body follows the same course as it does in the digestive tract—viz., albumoses, peptones, and amido-acids—has not yet been determined. Pathologically, at least, albumoses may be formed, for they are demonstrable in the urine, as will be shown in discussing the subject of fever (p. 388).

Autolysis.—If the organs of the body are kept aseptically at 37° C. for some time, their proteids undergo hydrolytic cleavage, owing to the action of enzymes that are present in

the cells.[44] Albumoses have not been demonstrated as products of this " autolysis," presumably because they are so rapidly split up into amido-acids, basic substances, fatty acids, hydrogen sulphide, carbohydrates, etc. The nucleo-proteids are decomposed into proteids and the nucleinic acids, and the latter decompose again into phosphoric acid and the purin bases. It is an interesting fact that the enzymes in any particular class of cells will split up the proteids of those cells more readily than they will split proteids from other sources. To what extent the cleavage of proteids within the normal body resembles autolysis is not known, for normally the intermediary products of proteid catabolism, such as the amido-acids, do not appear in the urine.

The products of a hydrolytic cleavage of proteids are, however, excreted under pathological conditions, especially when dead cells or fibrin are left to themselves; as occurs in abscesses, in the resolving stage of pneumonia,[45] in acute yellow atrophy of the liver, and in phosphorus poisoning. In all of these, albumoses and even peptones may appear in the urine.[46]

Since the above conditions are caused by toxic or infectious processes, the question naturally arises as to whether the hydrolytic cleavage of the proteids is due directly to the toxins or bacteria that cause the disease, or whether it is due to the action of the intracellular enzymes and is of the nature of an autolysis. The former view seems rather improbable, for Müller has shown that the pneumonic exudate exhibits no tendency to undergo hydrolytic cleavage so long as but few leucocytes are present, even though the bacteria have been

[44] Salkowski, Deut. Klinik., vol. xi. p. 147.

[45] F. Müller, Kongr. f. in. Med., 1902, p. 192; Simon, Arch. f. klin. Med., vol. lxx. p. 604.

[46] For pneumonia, see Ito, Arch. f. klin. Med., vol. lxxi. p. 29; for albumosuria in general, see Stadelmann, Untersuchungen über Peptonuria, Wiesbaden, 1894.

there all the time. As has been already mentioned, the tissues, free of all bacteria, contain proteolytic enzymes, and it seems probable that these are responsible for the abnormal decompositions in the above-mentioned conditions.

During the involution of the puerperal uterus the muscle-fibres also undergo autolysis,[47] and the resulting products may appear in the urine.[48]

In many diseases of the liver no abnormal end-products of proteid decomposition are excreted. In other more serious hepatic conditions, various pathological substances appear, and in acute yellow atrophy and phosphorus poisoning, especially, the urine may contain albumoses,[49] or even peptones,[50] as well as leucin, tyrosin, para-oxyphenylacetic acid, and lysin.[51] These substances appear to arise mainly from an autolysis of the liver cells, but in some cases the quantity in the blood is so great that they could not possibly have all originated in this manner, and some must have come from other tissues.[52]

The Formation and Excretion of Ammonia.—Normally, from two to five per cent. of the total nitrogen excreted appears in the urine in the form of ammonium salts. Under pathological conditions, however, the proportion may be greatly increased, and in acute yellow atrophy, for example, it may even reach thirty-seven per cent.

An increased excretion of ammonia is not the result of an increased production of this compound within the body; for large quantities of the ammonium salts of organic acids

[47] Langstein and Neubauer, Münch. med. Wochens., 1902, p. 1249.

[48] Ehrström, Arch. f. Gyn., vol. lxiii. p. 695.

[49] v. Jaksch, Ztft. f. klin. Med., vol. vi. p. 413; Robitschek, Deut. med. Wochens., 1893, No. 24.

[50] Miura, Virch Arch., vol. ci. p. 317.

[51] Neuberg and Richter, Deut. med. Wochens., 1904, No. 14.

[52] A. E. Taylor, Jour. of Med. Research, vol. viii. p. 424; Neuberg and Richter, Deut. med. Wochens., 1904, p. 499.

may be taken by the mouth with only an insignificant increase in their elimination in the urine.[53] The quantity of ammonium salts in the urine is to be regarded rather as an indication of an excessive quantity of acid in the body. The ammonia normally formed in metabolism, instead of being transformed into urea, combines with the excessive acids, and is excreted by the kidneys as the ammonium salts of these acids. For example, Walter [54] found that, after administering hydrochloric acid to dogs, about three-fourths of it was neutralized by ammonia in the body, while most of the remainder went to raise the acidity of the urine, and a small part apparently combined with the fixed alkalies of the blood. This last effect is serious, for the ability of the blood to carry carbon dioxide is thereby diminished (see p. 228).

An excessive excretion of ammonia is indicative, therefore, of an excessive amount of acid in the body. The amount of ammonia in the urine is increased whenever the proteids of the diet are increased at the expense of the carbohydrates, for the reason that proteids furnish an acid ash. The amount is increased, furthermore, whenever there is a pathological breaking down of the tissues, for this is equivalent to an increased proteid catabolism. In diabetes, an excessive amount of organic acids may be formed, thus increasing the elimination of ammonium salts.[55] Finally, an abnormal excretion of ammonia may accompany various chronic diseases, especially of the liver.

That the increased elimination of ammonia is purely secondary has been proved by the fact that, if alkalies be administered to patients who excrete excessive quantities of ammonia in the urine, the abnormal acid in the body will be

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[53] Rumpf, Kongr. f. in. Med., 1896, p. 509; also Virch. Arch., vol. cxliii. p. 1.

[54] Arch. f. exp. Path., vol. vii. p. 148.

[55] Rumpf, Virch. Arch., vol. cxliii. p. 1.

neutralized, the excessive excretion of ammonium compounds diminished, and the excretion of urea correspondingly increased.

In some instances the origin of the abnormal acidity is readily determined. Mineral acids may have been taken by mouth, either accidentally or with suicidal intent. In phosphorus poisoning, the rapid destruction of cell protoplasm liberates the sulphur and phosphorus contained in the proteid molecules, and these give rise to sulphuric and phosphoric acids in considerable quantities. In addition to these, various organic acids, such as lactic and aromatic acids, are formed in phosphorus poisoning, and this excessive acid production is sufficient to account for the increased excretion of ammonia which takes place in this condition. In many diseases, however, we can only surmise the cause of the excessive production of acids in the body.

The Production of Organic Acids.—Organic acids, especially carbonic and carbamic acids, are being constantly formed in normal metabolism. These particular acids, however, are not eliminated in ammonia combinations, for the carbonic acid leaves the body, for the most part, through the lungs, and the ammonium salt of carbamic acid can be transformed into urea in the liver. The organic acids that are most frequently eliminated as ammonium compounds are β-oxybutyric and diacetic acids.

It is remarkable that sarcolactic acid is not more frequently found in the urine, for we know that it is normally formed in considerable quantity during muscular activity. Under such circumstances, however, it is apparently rapidly oxidized. It probably arises from the non-nitrogenous products of proteid cleavage, although it is possible that it may also arise in part from the carbohydrates. Pathologically, lactic acid has been found in the urine in cases of phosphorus poisoning,[56]

[56] v. Noorden, Stoffwechselpathologie, p. 294.

in trichinosis,[57] in pernicious anæmia, in severe heart disease, acute yellow atrophy, and typhoid fever,[58] and in animals during arsenical poisoning.[59] Yet in none of these conditions, with the possible exceptions of phosphorus poisoning and acute yellow atrophy, does lactic acid regularly appear in the urine. In some, its appearance is possibly due to a diminution in the oxidative processes within the body; in others, to disease of the liver; and, in still others, to unknown causes. Æthyliden-lactic acid has been found in the urine in severe cases of diabetes, and at times proprionic and acetic acids have also been found.

Of all the organic acids, β-oxybutyric is the most important in this respect, for it appears in the urine not so very infrequently, and sometimes it is excreted in enormous quantities. If this acid be oxidized, it is transformed into diacetic acid, and later into aceton, so that these three substances are very closely related, and they have been collectively termed the aceton bodies.[60] All three are excreted by the kidneys, and, in addition, aceton may leave the body with the expired air, giving a characteristic "fruity" odor to the breath. Normally, these aceton bodies are oxidized to carbon dioxide and water in the body, and only traces, at most, of aceton are normally excreted in the urine. Under various abnormal conditions, however, they may leave the body unoxidized. This may occur during hunger,[61] during a salt-free diet,[62] in many cases of diabetes,[63] and in some cases of fever[64] and of car-

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[57] Wiebel, Ber. k. k. chem. Gesellsch., 1871, p. 139.

[58] v. Noorden, loc. cit.

[59] H. Meyer, Arch. f. exp. Path., vol. xvii. p. 304.

[60] Waldvogel, Die Acetonkörper, Stuttgart, 1903.

[61] Lehmann, Müller, et al., Virch. Arch., vol. cxxxi. Suppl.

[62] A. H. Taylor, Univ. of Cal. Publications, Pathology.

[63] Stadelmann, Arch. f. exp. Path., vol. xvii. p. 419; Minkowski, ibid., vol. xviii. p. 35.

[64] Kulz, Ztft. f. Biol., vol. xxiii. p. 165.

cinoma.[65] Experimentally, β-oxybutyric acid may appear in the urine of dogs after phloridzin poisoning and after extirpation of the pancreas,[66] though the latter is rare. At times some one or several of these compounds, but especially aceton, will appear in the urine without any cause.[67] It is possible, in these obscure cases, that it arises from the absorption of toxic substances from the intestines. It was formerly held that the aceton bodies might be formed within the intestinal canal, but at present there is but little inclination to refer their origin to this source. In the majority of cases, at least, they are produced during the intermediary metabolism within the body.

No strict parallelism seems to exist between the amount of aceton bodies and the rapidity of proteid decomposition, and it is possible, for example, to find β-oxybutyric acid in the urine at a time when the body is in nitrogenous equilibrium.[68]

One important cause that leads to the formation of the aceton bodies is a diminution in carbohydrate metabolism with an increased destruction of fats. For this reason, they are very apt to appear in the urine during fasting; and it has been shown that the administration of fats and especially of fatty acids by the mouth increases their elimination.[69] Many favor the view that aceton, diacetic acid, and β-oxybutyric acid are all derived from the breaking down of fat in the body; but, owing to our ignorance as to the relation that exists between the carbohydrates, the fats, and the non-nitrogenous cleavage products of the proteids, it is impossible at present to reach a final verdict on this question.

[65] Klemperer, Berl. klin. Wochens., 1889, No. 40.

[66] v. Mering, Ztft. f. klin. Med., vol. xvi. p. 431; Minkowski, Arch. f. exp. Path., vol. xxxi. p. 85.

[67] Lorenz, Ztft. f. klin. Med., vol. xix. p. 18.

[68] Weintraud, Arch. f. exp. Path., vol. xxxiv. p. 169.

[69] Joslin, Jour. of Med. Research, vol. xii. p. 433.

In no disease do the aceton bodies appear in the urine in such large quantities as they do in some cases of diabetes mellitus. Their formation in this condition is undoubtedly in part dependent upon an inability to consume carbohydrates normally and upon the resulting excessive consumption of fats; yet these factors are certainly not the only ones present, for in many severe cases of diabetes the aceton bodies are absent from the urine. This appears to be especially true of pancreatic diabetes.[70]

The Effects of an Excessive Formation of Organic Acids. Diabetic and Other Toxic Comas.—The specific action of the aceton bodies is a comparatively slight one. Aceton, in large doses, will produce a sort of drunkenness, similar to that caused by alcohol, and it is possible that in certain intestinal diseases of children it may cause a feeling of fatigue. The effect produced by β-oxybutyric and diacetic acids is, for the most part, not a specific toxic effect of these compounds, but is due to their acid properties. (That this is not altogether true is proved by the fact that neutral salts of β-oxybutyric acid are somewhat toxic to rabbits.[71]—ED.) In virtue of their acid properties, these organic acids will combine with basic substances in the body, and they tend to carry them away in the urine. In this manner they produce the symptoms of an acid intoxication (see p. 228).

In the comas that accompany diabetes, carcinoma, and some intestinal diseases, large quantities of β-oxybutyric acid are usually eliminated in the urine. The patient becomes stupid and sleepy or, at times, irritable. The temperature falls, the respirations become deep and often more frequent, and the heart's action becomes rapid.

The immediate cause of diabetic coma is unknown, but it seems to be precipitated in some instances by a too rigorous

[70] Lüthje, Personal communication.
[71] R. Wilbur, Jour. of the Am. Med. Assoc., 1904, p. 1228.

meat diet, or, again, by digestive disturbances. The symptoms are certainly very similar to those that result from acid intoxications experimentally produced, and in no other condition are such enormous quantities of β-oxybutyric acid found in the urine as at the onset of diabetic coma The ability of the blood to carry carbon dioxide is usually found to be considerably diminished [72] during diabetic coma, just as it is in experimental acid intoxications (see p. 228). These facts indicate the acid character of the intoxication.

On the other hand, in some comas, complicating diabetes, no increased elimination of acids has been found.[73] Yet such cases are quite rare; and, as a rule, the symptoms of diabetic coma are accompanied by an acid intoxication.[74] The coma is preceded by an increased formation of β-oxybutyric acid in the body, and large quantities of this acid may appear in the urine as the ammonium salt. During the coma, however, the elimination frequently does not keep pace with the acid formation, and consequently considerable amounts are retained in the body. Careful estimations of the amounts thus retained demonstrate that they are sufficient to give rise to coma. In some cases, it is possible to abort the coma, partly or completely, by the use of large quantities of soda, which serves to neutralize the acid in the body.[75]

Those rare cases of diabetic coma without increased acid formation are, according to Naunyn, produced by other toxic substances, which directly act upon the cerebral cells, and especially upon the cells of the respiratory centre. The exact nature of these toxic substances is unknown, but from the diversity of symptoms seen in diabetic coma it is readily conceivable that more than one cause is operative.

[72] Kraus, Ztft. f. Heilkunde, vol. x. p. 106.
[73] Kraus, loc. cit , Rumpf, Berl klin. Wochens., 1895, Nos 31 and 32.
[74] Magnus-Levy, Arch. f. exp. Path , vol. xlii. p. 149; vol. xlv. p. 389.
[75] Lüthje, Ztft. f. klin. Med., vol. xliii p 225.

The Relation between Hepatic Disease and the Excretion of Ammonia.—The greater portion of the nitrogenous waste, which does not serve to neutralize acids, leaves the body in the form of urea. We know that the liver can convert many ammonium salts, such as the carbamates, into urea, and Minkowski's experiments on birds would seem to indicate that this is a portion of the normal hepatic function.[76] On the other hand, we are not certain that all the eliminated urea is thus formed in the liver, nor, indeed, that it is all derived from ammonium salts.

These questions are of the greatest importance, for it is possible that some relation may exist between hepatic diseases, on the one hand, and the amount of urea formed out of ammonium salts, on the other. Not infrequently it happens that the liver is found to be diseased when large quantities of ammonia have appeared in the urine. We have seen that one cause of an increased excretion of ammonia is an acid intoxication, in which case the ammonia serves merely to neutralize the excess of acid. Is it not possible, however, that large amounts of ammonia may be excreted for the reason that the liver is so diseased that it cannot form urea out of ammonium salts? Such a serious loss of function could only result from a most extensive destruction of liver cells, if we may draw any analogy from the corresponding effects produced by diseases of the pancreas and of the thyroid gland.

An increased excretion of ammonium compounds at the expense of urea has been observed in different forms of hepatic disease, such as cirrhosis, tumors, and extensive degenerations, though these urinary changes do not accompany all serious diseases of the liver.[77] Weintraud discovered that if ammonium salts were administered to patients, even in the advanced stages of hepatic disease, these salts were converted into urea

[76] Minkowski, Arch. f. exp. Path., vol. xxxi. p. 214.
[77] Weintraud, ibid., p. 30; Munzer, ibid., vol. xxxiii. p. 180.

just as they are in healthy individuals; thus demonstrating that these patients are still able to transform large quantities of ammonium salts. It therefore seems very probable that the excessive ammonia in their urine is due to an abnormal production of acids in their bodies. As yet, however, their elimination of acid substances has not been sufficiently investigated. If the excretion of ammonium salts could be decreased by the administration of fixed alkalies, then we could feel fairly certain that in all these hepatic diseases we were again dealing with a primary acid intoxication, similar to that present in diabetic coma.

Alkaptonuria.—The tyrosin and phenylalanin groups of the proteid molecules at times give rise to the formation of dioxyphenylacetic acid (homogentisic acid), and to dioxy-phenyl lactic acid (hydrochinonlactic acid). When these acids are excreted by the kidneys, the urine turns dark on standing or on the addition of alkalies, and the condition is termed alkaptonuria.[78] These urines will reduce Fehling's solution, and the condition may be mistaken for a glycosuria. Patients with alkaptonuria show no other clinical peculiarities, save occasionally a pigmentation of the cartilages in various parts of the body. Although the belief was held at one time that the substances giving rise to the reaction for alkapton were produced in the intestines, it now seems certain that these oxyacids arise within the body during intermediary metabolism, and that they appear in the urine because the organism is unable to break down the tyrosin and alanin groups of the proteid molecule in a normal manner. If tyrosin be administered to these patients, it appears in the urine as alkapton, and, since tyrosin is believed to be one of the products of

[78] Baumann and Wolkow, Ztft. f. physiol. Chem., vol. xv. p. 228; E. Meyer, Arch. f. klin. Med., vol. lxx. p. 443; Langstein and Meyer, ibid., vol lxxviii. p. 161; Mittelbach, ibid., vol. lxxi. p 50, Abderhalden and Falta, Ztft. f. physiol Chem., vol xxxix. p 143.

normal proteid catabolism, the amount of alkapton which appears in the urine in these patients is an indication of the amount of proteid metabolism. The real reason why the body is unable to break down the tyrosin group is unknown to us, as is the organ in which this group is transformed into the alkapton acids.

CHAPTER VIII.

DISTURBANCES IN CARBOHYDRATE METABOLISM. DIABETES.

IN this chapter we shall limit our discussion to dextrose or grape-sugar; for, although other sugars, such as levulose [1] and pentose [2] may appear in the urine, nevertheless the meaning of these findings is not yet sufficiently clear to be discussed in connection with dextrose.

The cells of the body that use dextrose, especially the muscle-cells, take it out of the blood; yet the amount in the plasma remains nearly constant, for whenever the percentage falls below the normal, new sugar is supplied to the blood, mainly from the glycogen storage in the liver. The liver glycogen is derived, for the most part, from the carbohydrates, and, to a lesser extent, from the proteids taken in the food. The sugar that is absorbed from the intestines goes to the liver by way of the portal vein, and is there converted into glycogen by a process of dehydration and polymerization. The non-nitrogenous products of proteid cleavage may also apparently be converted into glycogen by a synthetic process, though this is denied by some.[3] The liver acts, therefore, as a store-house for carbohydrate material, holding it back when it is present in the blood in excess, and giving it out when the percentage falls.

In a healthy man the sugar in the blood varies but little, the quantity remaining constantly in the neighborhood of 0.1 to 0.2 per cent. If, for any reason, more than this is present in the general circulation without being immediately consumed,

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[1] Müller, Path. der Ernährung, p. 232.

[2] Kulz & Vogel, Ztft. f. Biol., vol. xxxii. p. 185; Salkowski, Berl. klin. Wochens., 1895, No. 17; Blumenthal, ibid., No. 26.

[3] Pflüger, Pflüger's Arch., vol. xcvi.

it is eliminated by the kidneys, and the urine then contains more than the trace of dextrose normally present.

Alimentary Glycosuria.—As we have said, the liver possesses the property of removing from the portal blood any excessive quantity of sugar that may be present there. If, for example, a limited quantity of dextrose be injected into the portal vein, the excess disappears from the blood; whereas, if the same quantity be injected into a systemic vein, the percentage in the general circulation is increased and sugar is excreted by the kidneys.[4]

Yet, when very large amounts of dextrose are taken by mouth and are absorbed from the intestinal canal within a short space of time, the percentage in the blood may rise above the normal, either because the liver cannot stop all the sugar coming to it through the portal vein or because some sugar reaches the general circulation through the lymphatics without traversing the liver.[5] Under such circumstances dextrose may be excreted by the kidneys, and we speak of this condition as an alimentary glycosuria. The quantity of sugar that must be taken by mouth in order to produce an alimentary glycosuria varies in different individuals.[6] It does not necessarily follow, however, that a certain person is in an early stage of diabetes merely because he passes dextrose in the urine after taking a relatively small quantity by mouth.[7] Yet such may be the case. Minkowski has shown, for example, that whereas the removal of the whole of the pancreas is followed by a diabetes, the removal of a part may cause merely an inability to take much sugar in the food without having it appear in the urine. Furthermore, clinical experience has demonstrated

[4] Schöpffer, Arch. f. exp. Path., vol. i. p. 73.

[5] Ginsberg, Pflüger's Arch., vol. xliv. p. 306.

[6] Hofmeister, Arch. f. exp. Path., vol. xxv. p. 240; see v. Noorden, Pathologie der Soffwechsels, p. 391.

[7] Strauss, Deut. med. Wochens., 1897, Nos. 18 and 20.

that, in some cases, a marked alimentary glycosuria gradually passes on into a true diabetes mellitus.

The occurrence of an alimentary glycosuria in a healthy man is greatly favored by alcoholic drinks, and especially by the ingestion of large quantities of beer.[8] It is impossible to say why this should be so, and whether the effect, in the case of beer, is to be attributed more to its alcohol or to its maltose.

Lactose may also appear in the urine after excessive quantities have been taken in the food, but it appears there more frequently because it has been resorbed from the mammary glands of nursing women, owing to a stasis of milk. Some special factor seems to favor its excretion in these cases, for the amount absorbed would appear to be too small to give rise to an ordinary alimentary glycosuria.

Many studies have been made upon the ease with which an alimentary glycosuria may be produced in different diseases. Apparently, it is most apt to follow the ingestion of a small quantity of sugar when the patient is suffering from phosphorus poisoning or from some infectious disease, and an alimentary glycosuria is easily produced in certain patients with exophthalmic goitre and with various neuroses. Hepatic diseases apparently do not especially favor the development of a glycosuria after the administration of ordinary dextrose, but they frequently diminish the patient's ability to eat levulose without having it appear in the urine (alimentary levulosuria).[9]

Phloridzin Glycosuria.[10]—The glycosuria that follows the administration of phloridzin is peculiar, in that, according to

[8] Strumpell, Berl. klin. Wochens., 1896, No. 47; Krehl, Ztrbl. f. in Med., 1897, p. 103.

[9] Strauss, Deut. med. Wochens., 1901, Nos. 44 and 45; Chajes, ibid., 1904, No. 19.

[10] See v. Mering, Kongr. f. in Med., 1886, p. 185; Minkowski, Arch. f. exp. Path., vol. xxxi. p. 85; papers by Lusk *et al.*, in Am. Jour. of Physiol., vols. i., iii., ix., and x.

most observers, it is accompanied by a normal or reduced percentage of dextrose in the blood.[11] Chemically, phloridzin is a glucoside,—*i.e.*, it is capable of being split up into dextrose and a proteid radicle. The amount of dextrose that appears in the urine after the administration of phloridzin, however, is so great that it cannot be accounted for by a mere splitting of the glucoside, and it is certain that the administration of this substance will result in an actual removal of dextrose from the body. In what manner is this accomplished? According to one view, the resulting glycosuria is caused by some alteration in the cells of the kidneys, whereby they become permeable for the sugar normally present in the blood. According to another view, however, the glucoside decomposes in the kidneys and the glucose derived from it is eliminated. The other product of the decomposition, phloretin, then combines with the glucose of the blood and is again decomposed in the kidneys, and thus, by acting as a carrier of glucose, phloridzin may cause the excretion of large quantities of sugar.

In phloridzin poisoning the sugar excreted is derived, first of all, from the glycogen of the liver, which early disappears. It seems probable that it may also be derived from the proteids of the body, for it is known that glucose continues to be excreted in phloridzin poisoning, even though the animal be fasting and its liver presumably free of glycogen. At any rate, the proteid decomposition is accelerated under these circumstances, and even β-oxybutyric acid may be excreted.[12] If phloridzin be given to fasting animals, a fatty degeneration of the liver is produced, which can be prevented if the animal be fed on proteids or carbohydrates.[13] At times the amount of sugar excreted after taking phloridzin is so great that it

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[11] In opposition, see Pavy, Jour. of Physiol., vol. xx., and Pflüger, Pflüger's Arch., vol. xcvi. p. 383.

[12] Praussnitz, Ztft. f. Biol., vol. xxix. p. 168.

[13] Rosenfeld, Ztft. f. klin. Med., xxviii. p. 256.

seems as if it must be formed in part from the fats of the body,[14] a possibility that will be considered in another place (p. 356).

Renal Diabetes.—The glycosuria of phloridzin poisoning is therefore characterized by the fact that the amount of sugar in the blood is not increased; and it seems probable that in this condition, as well as in certain cases of marked diuresis,[15] the resulting glycosuria is due to an inability on the part of the renal cells to hold back the sugar normally present in the blood. Little is known about such conditions in man, but recent observations have tended to show that glycosuria may result from just such a renal insufficiency. To these cases has been given the name of renal diabetes.[16] Lüthje has shown that the sugar was present in the blood of his patient in less than the normal quantity, thus demonstrating that the glycosuria was due to some abnormal permeability on the part of the kidneys toward dextrose. The amount of sugar excreted by such patients is independent, to a great extent, of the amount taken in the food; yet this is not especially characteristic of renal diabetes, for the same is true of certain forms of diabetes mellitus.

Transient Glycosurias.—Glycosurias, lasting only a few hours or days,[17] have been observed after various intoxications, infections, injuries, and diseases of the central nervous system.

Of these transient glycosurias, the best studied is that which results from a puncture of a certain limited area in the floor of the fourth ventricle of animals.[18] In these cases the appearance of sugar in the urine is always preceded by an

[14] Rumpf, Hartogh, and Schumn, Arch f exp. Path, vol xlv. p. 11.

[15] Jacobi, Arch f exp Path., vol xxxv. p 213; O. H Brown, Am Jour. of Physiol, vol. x. p 378.

[16] G. Klemperer, Berl. klin. Wochens., 1892, No. 49; Naunyn, Diabetes, p. 106; Lüthje, Munch. med Wochens., 1901, No. 38.

[17] Böhm and Hoffman, Arch. f exp. Path., vol. viii p. 297

[18] Claude Bernard, Pfluger, Pfluger's Arch, vol. lxxxvi pp. 303, 360.

increase in the amount present in the blood, and it is favored by a large store of glycogen in the liver. If glucose be injected into a mesenteric vein in these animals, it is not taken up by the liver as it normally should be, but it passes into the general circulation and is then excreted by the kidneys. If the splanchnic nerves be cut, or if the liver be removed, a puncture of the fourth ventricle has no effect upon the urine. All these facts seem to indicate that the glycogen of the liver is the source of the excessive amount of sugar in the blood and that the nervous lesion causes the glycosuria by influencing, in some manner, the glycogenic function of the liver.

The glycosurias that may accompany morphine and curare poisoning are apparently of a similar nature.

DIABETES MELLITUS.

Diabetes mellitus is characterized by a glycosuria that is not due to any of the above-mentioned causes, and especially not to the ingestion of large amounts of grape-sugar. Usually the dextrose is constantly present in the urine, but it may only be found there periodically. In some cases of diabetes, levulose also appears in the urine.[19] The glycosuria of diabetes mellitus always results from an excessive amount of sugar in the blood, a hyperglycæmia. Instead of the normal percentage of 0.1 to 0.2, it may rise even to 0.7 per cent.

Mild and Severe Diabetes.—In the milder forms of diabetes, sugar does not appear in the urine if no carbohydrates— *i.e.*, sugars, starches, etc.—are taken in the food. Great individual variations exist as to the quantity of carbohydrate material that must be taken in order to produce glycosuria. On the one hand, a patient may be able to take one hundred and fifty grams or more of starch in twenty-four hours without suffering from glycosuria; while, on the other, a glycosuria

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[19] May, Arch. f. klin. Med., vol. lvii. p. 279; Rosin and Laband, Ztft. f. klin. Med., vol. xlvii. p. 182; Naunyn, Diabetes.

may result when only twenty-five to thirty grams are taken. Not all carbohydrates show the same tendency to cause glycosuria in these patients, and many, for example, will tolerate lactose in the food even better than starch.

This mild form of diabetes is distinguishable from alimentary glycosuria by the fact that starch is not tolerated; for, so far as we know, a mere excess of starch in the diet of a normal individual never leads to the excretion of an abnormal quantity of sugar in the urine   Possibly, however, exceptions do occur to this rule, notably in the case of infectious diseases.

In the more severe forms of diabetes, sugar is excreted in the urine even when no carbohydrates are taken by mouth, and in some, the most severe cases, the glycosuria even continues when the patient is fasting.

It was formerly believed that this distinction between mild and severe cases of diabetes was a sharp one, and that it rested upon fundamental differences in the tissues. In the mild cases the body was unable to assimilate carbohydrate material introduced as such, but was able to consume the carbohydrate molecules split off from the proteids, whereas, in the severe cases neither could be utilized. Yet we now know that no such sharp distinction can be drawn, that the one condition shades into the other, and that, finally, the body may be able to consume a considerable proportion of the carbohydrates taken in the food, even though the diabetes is so severe that glycosuria persists during fasting. Notwithstanding these facts, the above distinction has a certain clinical value, and a case of diabetes can hardly be considered a mild one if the body is unable to assimilate a certain amount of carbohydrate material in the food without the excretion of sugar in the urine.

Derivation of Sugar from Proteids and Fats.—The sugar that appears in the urine in these severe cases of diabetes, when the patient is on a diet free of ordinary carbohydrates, is derived either from the glycogen or substances resembling

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glucosides within his own body,[20] or from the proteids or fats of the food or of the body. That sugar may be derived from proteids is a view widely accepted by both pathologists and physiologists. The amount excreted in severe cases of diabetes may be so great as to render it improbable that it could all have come from preformed carbohydrate groups of atoms within the proteid molecule. It is necessary to assume in these cases that the sugar has been synthesized in the body from other groups of atoms contained within the proteid molecules. Casein, for example, does not contain such preformed carbohydrate groups, yet its administration to certain diabetics increases the elimination of sugar as much or even more than does the administration of an equal quantity of proteids known to contain preformed carbohydrate groups.[21]

This view that sugar may arise from proteids containing no preformed carbohydrate groups has been strenuously opposed by Pflüger.[22] He considers that all the sugar excreted in the urine is derived from carbohydrates or from carbohydrate groups in the proteid molecules. It does not lie within our province to discuss the purely physiological side of this question; yet it seems proper for us to review some of the evidence bearing upon the question as to the ability of the pathological diabetic organism to form sugar out of proteids.

We possess no accurate data as to the quantity of glycogen stored up within the bodies of diabetic patients, and Pflüger has shown that the quantity is often underestimated. Nevertheless, a great number of observations would seem to indicate that the quantity of glycogen in the liver is diminished in diabetes.[23] If this were so, then the amount of sugar that

[20] Pflüger, Pflüger's Arch., vol. xcvi.

[21] Lüthje, Ztft. f. klin. Med., vol. xxxix. p. 397; vol. xliii. p. 225.

[22] Pflüger's Arch., vol. xlvi. p. 1.

[23] See Külz, Pflüger's Arch., vol. xiii. p. 267; v. Mering, ibid., vol. xiv. p. 274; Abeles, Zentralbl. f. die med. Wissen., 1885, No. 26; Naunyn, Diabetes.

patients with severe diabetes may excrete after the adminis-
tration of casein admits of hardly any other interpretation
that that it is derived from proteids.[24]   In dogs from which
the pancreases have been removed this is even more clear, for
the glycogen in their livers and muscles is always small, and
during fasting it practically disappears.[25]   Yet if casein be
given to these fasting dogs, sugar is immediately excreted in
the urine in quantities corresponding to the quantities of
casein that they have taken.[26]   Pflüger would explain many
such observations by assuming that the subject of the experi-
ment secretly took carbohydrates; yet, although this may
have occurred in a limited number of instances, it is highly
improbable that it could have occurred in all; and, to us, at
least, it seems practically certain that diabetics may form sugar
out of proteids that contain no preformed carbohydrate atomic
groups.[27]

It is not fully known in what parts of the body the sugar
is formed from proteids.   The liver is certainly one site of
such transformation, and possibly the muscles may exercise a
similar function.

Even though we thus assume that sugar may arise from
proteids, obscure cases still remain.   One hundred grams of
proteid material could, at most, give rise to about one hundred
and thirty grams of sugar and sixteen grams of nitrogen.
The ratio of dextrose to nitrogen (D:N) under these circum-
stances would be about 8 to 1.   As a matter of fact, the ratio
(D:N), as determined in the urine of dogs from which the
pancreases have been removed, and which were fed on a

[24] Külz, Arch. f. exp. Path., vol. vi. p. 140.

[25] Minkowski, Arch. f exp. Path., vol. xxxi. p. 161.

[26] Lüthje, Arch. f. klin Med., vol. lxxix. p. 488; Mering, ibid.,
vol. xiv. p. 274.

[27] A similar view is expressed by F. Müller, Path. der Ernährung; F.
Kraus, Berl. klin. Wochens., 1904, No. 1; Magnus-Levy, Verh. der physiol.
Gesell. zu Berlin, 1904, Nos. 5 and 8.

proteid diet, was found to be 2.8 to 1;[28] though recently, both in animals with phloridzin poisoning and in men with very severe diabetes, a somewhat higher ratio has been found,—about 3.7 to 1.[29] It has been assumed that the dogs deprived of their pancreases were incapable of consuming sugar, and that the ratio found (2.8 to 1) represented the total amount of sugar derived from the cleavage of the proteid molecules within the body. Yet this assumption has proved to be incorrect; for, if the dogs fast completely after the operation, the excretion of sugar gradually ceases, while the percentage in the blood returns to about normal. The bodies of these animals are therefore capable of consuming a limited quantity of sugar.[30]

In certain cases of phloridzin diabetes and of diabetes mellitus [31] the ratio (D:N) has been found to be as high as 6 to 1, or even higher. According to one explanation, an unusual amount of sugar is formed out of the proteids of the body in these cases; according to another explanation, the fat of the body is converted into sugar and is excreted as such. In this connection, it is proper to note that during the diabetes produced either by phloridzin [32] or by the excision of the pancreas,[33] the administration of glycerin or lecithin may increase the output of sugar. We have no direct evidence, however, that sugar may arise from fats; for the administration of fats does not affect the glycosuria.

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[28] Minkowski, Arch. f. exp. Path., vol. iii. p. 85.

[29] Mandel and Lusk, Arch. f. klin. Med., vol. lxxxi. p. 472.

[30] Lüthje, Münch. med. Wochens., 1902, No. 36.

[31] v. Mering, Ztft. f. klin. Med., vol. xvi. p. 431; Hartogh and Schumn, Arch. f. exp. Path., vol. xlv. p. 11; Rumpf, Pflüger's Arch., vol. xcvii. p. 98; Rosenquist, Berl. klin. Wochens., 1899, No. 28; Mohr, ibid., 1901, No. 36; Lüthje, Ztft. f. klin. Med., vol. xliii. p. 225; Rumpf, ibid., vol. xlv. p. 260.

[32] Cremer, Asher-Spiro Ergebnisse, vol. i. p. 888.

[33] Lüthje, Münch. med. Wochens., 1902, No. 39.

The Glycogenic Function of the Liver in Diabetes.—We have already stated that diabetes mellitus is always accompanied by an increased percentage of sugar in the blood, a hyperglycæmia. If the sugar appear in the urine only when carbohydrates are taken in the food, it is possible to explain the condition on the assumption that the liver does not store up the sugar coming to it by way of the portal vein, but allows it to raise the percentage in the blood. The capacity of the liver to form glycogen seems to be diminished in most cases of diabetes mellitus, and in some cases more than in others; which accounts, in part, for the different amounts of sugar that are excreted by different patients when all take equally large quantities of starch. On the other hand, the ability of the liver to pick sugar out of the portal blood and to store it never seems to be completely lost in diabetes. In a few mild cases this function does not seem to be greatly affected, for the amount of glucose in the urine remains fairly constant, even though considerable quantities of starch are taken in the food.

After experimental removal of the pancreas from dogs the capacity of the body for storing up carbohydrates is certainly diminished, for Minkowski has shown that in these animals the glycogen in the liver and muscles is always reduced, and that it disappears during fasting.[84]

As we have just said, the ability to ingest carbohydrates without having sugar appear in the urine varies greatly in different diabetic patients. This "assimilative capacity" may be influenced by various procedures, but especially by not over-taxing the organism with too much sugar. If, for example, a diabetic patient is able to take one hundred grams of bread daily without having glycosuria, and if he has kept within this limit for several months, he may then be able to take one hundred and twenty or one hundred and forty grams of bread

[84] Minkowski, Arch f. exp. Path., vol xxxi. p. 161.

with impunity. In this manner diabetic patients may be greatly benefited by treatment.

In severe cases of diabetes, the patient frequently excretes much more sugar than would correspond to the carbohydrates taken in the food, the extra sugar being derived, in all probability, from proteids. If the formation of sugar from proteids is a physiological process, then we may assume that there is a more or less fundamental difference between the two forms of diabetes. In the mild form the body cannot assimilate fully the sugar which is derived from the carbohydrates of the food, but can assimilate that derived from the proteids; whereas, in the severe form the assimilation of sugar derived from either source is diminished. There are patients who appear to justify such a distinction, for they are able to take large quantities of proteids without the appearance of sugar in the urine, but yet they react to the smallest quantity of bread with a glycosuria. In such cases, at least, it seems as if the sugar that arises from the proteids acted differently from that derived from the carbohydrates.

The Consumption of Sugar in Diabetes.—We now come to the question as to whether the diabetic body is able to burn sugar normally. Investigations on the respiratory interchange of gases have furnished evidence that the oxidation of sugar in certain diabetic patients is diminished.[35] We know that when carbohydrates are completely burned, the volume of carbon dioxide given off is equal to the volume of oxygen consumed; *i.e.*, the respiratory quotient is 1.0. For the combustion of proteids and fats, however, relatively more oxygen is necessary; and in the case of the higher fats the ratio of

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[35] Leo, Ztft. f. klin. Med., vol. xix. Supplement, p. 110; ibid., Kongr. f. in Med., 1889, p. 354; Weintraud and Leyes, Ztft. f. phys. Chem., vol. xix. pp. 603, 629; F. Voit, Ztft. f. Biol., vol. xxix. p. 129; Nehring and Schmoll, Ztft. f. klin. Med., vol. xxxi. p. 59; Magnus-Levy, Verhand. d. physiol Gesell. zu. Berlin, 1904, Nos. 5 and 7.

carbon dioxide to oxygen is about 1 to 2, or 0.5. When carbo-
hydrates are the main source of energy to the body, therefore,
the ratio between the carbon dioxide given off and the oxygen
absorbed approaches 1.0; whereas, when fats and proteids
furnish most of the energy, this ratio falls. It has been found
that diabetic patients upon an ordinary mixed diet show a
lower respiratory quotient than do normal individuals upon
the same diet. From this fact it may be inferred that, in
spite of the large amount of glucose circulating in their blood,
the utilization of carbohydrate material by diabetic patients
is deficient, and that the most of their energy is derived from
fats and proteids.

It appears, also, that this change in the respiratory quo-
tient is more marked in the severe than in the mild forms of
diabetes; in other words, the former burn sugar less than the
latter. This view is also supported by the effect that muscular
exercise has upon the excretion of sugar. In the milder forms
of the disease, muscular exercise tends to diminish the glyco-
suria, apparently because the body utilizes the sugar circulating
in the blood. In the more severe cases, on the other hand,
muscular exercise exerts but little effect upon the glycosuria,
for the body can utilize comparatively little sugar.

Thus we see that there is not only an insufficiency of the
glycogen reservoirs in diabetes, which permits an excess of
sugar to enter the circulation, but that there is, in addition, a
lessened ability on the part of the body to burn the sugar.

The nature of this lessened capacity for consuming sugar
is not well understood. Unfortunately, we know little con-
cerning the manner in which sugar is normally utilized in
the body or concerning the intermediary stages, such as
lactic acid or glycouronic acid, through which it may pass.
There seems to be no general diminution in the oxidative
ability of the body, for such substances as benzol,[38] lactic

[38] Reyher, Diss. Dorpat., 1885.

acid,[87] fat, and frequently even levulose are consumed normally. Diabetes consists rather in a specific limitation of the ability to consume dextrose, and it seems as if the diabetic body fails especially to initiate the combustion of this sugar. Nor is this all. Normally, carbohydrates can be converted into fat in the body, but in diabetes this power is diminished or lost.

We are acquainted with at least one factor that is necessary for a proper combustion of the sugar in the body. It is the pancreas. If this gland be extirpated from dogs, their ability to burn sugars is certainly diminished.[38] The same holds true also for carnivorous birds [39] and for reptiles and amphibia.[40] When a small portion of the pancreas is left at an operation, an alimentary glycosuria or a diabetes of the milder type may result, whereas, if the whole gland be excised, a diabetes of the severe type is the consequence. The sugar then accumulates in the blood, and the dextrose that is taken by mouth is again excreted in the urine. When an animal with such a pancreatic diabetes is placed on a strict meat diet, or when it is studied during the first few days of complete starvation, the ratio between the amounts of sugar and nitrogen excreted in the urine (D : N) is found to be 2.8 to 1. It has been assumed that these animals are utterly incapable of burning any dextrose, and that the above ratio represents the total amount of sugar formed in the body from the proteid molecule. Yet this assumption is incorrect, for Lüthje has shown that in the later stages of fasting the sugar will completely disappear from the urine of these dogs and the per-

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[87] Nencki and Sieber, Ztft. f. prak. Chem., vol. xxvi.

[38] v. Mering and Minkowski, Arch. f. exp. Path., vol. xxvi. p. 371; Minkowski, ibid., vol. xxxi. p. 85; Sandmeyer, Ztft. f. Biol., vol. xxxi. p. 12.

[39] Weintraud, Arch. f. exp. Path., vol. xxxiv. p. 303.

[40] Aldehoff, Ztft. f. Biol., vol. xxviii. p. 293.

centage of sugar in the blood will be normal.[41]   From this, we must infer that, even without a pancreas, it is possible for an animal to consume a certain amount of sugar, and that the ratio of 2.8 to 1 does not necessarily represent the total amount of sugar derived from proteids.

Pancreatic extracts do not possess any very decided action upon dextrose.   If, however, they are mixed with extracts from muscular tissues, which latter alone are also inert, then the mixture possesses decided glycolytic properties.[42]   It would appear from this that the pancreas produces an internal secretion which can assist the muscles in their consumption of sugar.

Such, in brief, are the main facts concerning the nature of diabetes.   Before an attempt is made to discuss them as a whole, however, it seems best to consider some other aspects of the disease.

The Etiology of Diabetes.—The tendency to acquire diabetes may be inherited, not alone from parents that have had the disease itself, but also from those who have had gout, obesity, or nervous disorders.

Diabetes sometimes follows severe cerebral concussions and injuries, as well as violent fright and other psychic traumata.   Arteriosclerosis and syphilis are frequently associated with diabetes, though we do not know whether they cause it by their action upon the nervous system or not.   Definite anatomical lesions of the brain, especially when situated in the neighborhood of the fourth ventricle, certainly can produce diabetes, though this is a very rare event.

At times diabetes is accompanied by diseases of the liver or pancreas; yet in the great majority of cases such diseases are not demonstrable, either during life or at autopsy.

The condition of the pancreas in diabetes is of especial

[41] Lüthje, Munch. med. Wochens., 1903, p. 1537.
[42] Cohnheim, Ztft. f physiol. Chem., vol. xxxi. p. 336.

interest on account of the glycosuria produced by an extirpation of this gland from animals. No pancreatic changes have been found post mortem in most diabetic patients, though, in some, easily recognizable changes were present.[43] If the pancreas is completely destroyed by disease, without leading to death within the first twenty-four hours, diabetes always develops. Primary carcinomata of the pancreas, however, may completely destroy the gland without producing diabetes; apparently because the carcinoma itself retains some of the functions of the normal tissues. We have already noted Naunyn's analogous observation,—i.e., that a carcinoma of the liver may secrete bile.

(It has been claimed recently that lesions of the islands of Langerhans in the pancreas cause many cases of diabetes. Opie, indeed, believes that more than half of all cases are of pancreatic origin, and that, when diabetes does result from pancreatic disease, an injury to the islands of Langerhans is responsible for the disturbance of carbohydrate metabolism.[44] In view of these recent observations, it is necessary to regard the statements of the earlier writers as to the frequency of pancreatic changes in diabetes with a certain amount of caution, for obviously their attention was not directed especially to these structures.—ED.)

Effects of Diabetes upon the Body.—In diabetes, a certain proportion of the energy taken in the food is not utilized by the body, and it is therefore necessary to cover the loss by more abundant nourishment. Even in severe forms of the disease the loss of carbohydrates may be covered by the administration of large amounts of fats and proteids, providing, of course, that the gastro-intestinal canal can absorb a necessary

[43] v. Hansemann, Ztft. f. klin. Med., vol. xxvi. p. 191; Hoppe-Seyler, Arch. f. klin. Med., vol. clii. p. 171; M. B. Schmdt, Münch. med. Wochens., 1902, No. 2.
[44] Diseases of the Pancreas, 1903, p. 279.

amount of material. Fortunately, this is usually possible, and only rarely is absorption markedly reduced in diabetes.[45] The greater an individual's need for energy, the more difficult will it be to maintain his nutrition when his ability to utilize carbohydrates is lessened. Yet the combined skill of physician and cook will often accomplish wonders in this respect. If the diabetic patient absorbs sufficient nourishment, his metabolism does not, as a rule, differ from that of a healthy individual upon the same diet. If it is impossible to furnish sufficient energy to him, his fat and body proteids are consumed, just as those are of a healthy individual during partial starvation. Some diabetics consume the proteid material in their bodies with abnormal rapidity, being similar in this respect to certain patients with malignant tumors and with cachexia.[46] Under these circumstances, it is naturally extremely difficult to maintain a nitrogenous equilibrium. From what has been said, it will be seen that in the severer forms of diabetes malnutrition frequently develops; for the patient is either unwilling or unable to take a sufficient quantity of fats and proteids to cover his total needs, and, in addition, his consumption of proteid material is sometimes abnormally rapid.

The metabolism in diabetic patients frequently shows other peculiarities as the disease becomes more advanced. Various organic acids, especially β-oxybutyric and diacetic acids are formed in the body. Indeed, they are produced in such quantities in no other condition as in some cases of diabetes mellitus. We have already stated that when an excessive amount of acid is present in the body, it is neutralized by the ammonia which would otherwise have been converted into urea (p. 338). For this reason the excretion of organic acids in diabetes is associated with an increased elimination of ammonia in the

[45] Hirschfeld, Ztft. f. klin. Med., vol. xix. pp. 294, 325; Pautz, Ztft. f. Biol., vol. xxxii. p. 197.

[46] v. Mering, Kongr. f. in. Med., 1886, p. 188.

urine. The source of the aceton and of the diacetic and β-oxybutyric acids is of great theoretical and practical interest, for the resulting acidosis is apparently the most important cause of the dreaded diabetic coma (see p. 342). Unfortunately, however, the cause of the acidosis and the source of the acids is but little understood (see p. 342).

In diabetes the nutrition of different parts of the body suffers in various ways. The crystalline lens of the eye may become opaque (diabetic cataract), and degenerations of the retina and choroid coat may develop. The arteries are often found to be sclerotic. (In some cases this is to be regarded as the cause rather than as the effect of the diabetes; for it is associated with degenerative changes in the islands of Langerhans.[47]—Ed.)

Tissues that are permeated with sugar seem to offer an excellent medium for the growth of micro-organisms, and it is well known how frequently diabetics become infected and how often these infections terminate in gangrene. The diabetic gangrene is due, in part, to the presence of excessive amounts of sugar in the tissue, and, in part, to the diminished blood-supply caused by an associated arteriosclerosis.[48] Patients with diabetes are furthermore very susceptible to tuberculosis, and here again the process shows a special tendency to develop into gangrene. Other complications, such as furunculosis, caries of the teeth, gingivitis, and stomatitis, are also frequently present in diabetic patients (see p. 231).

We know comparatively little concerning the relation that lesions of the kidneys bear to diabetes mellitus. Albuminuria is a not infrequent complication of the disease. In some cases it is due to a true nephritis, produced by the same cause which gave rise to the diabetes, such as arteriosclerosis, for example; in other cases it is apparently quite an accidental complication.

[47] See Hoppe-Seyler, Arch. f. klin. Med., vol. lxxxi. p. 119.
[48] König, Berl. klin. Wochens., 1896, No. 25.

When the albuminuria develops late in the diabetes, it may be questioned whether the continuous passage of sugar through the kidneys has not directly harmed the secreting cells. In this connection we may recall the glycogenic degeneration of the kidney so often found in diabetes.[49] The immediate cause of this degeneration and its relation to albuminuria are, however, insufficiently understood. That primary lesions of the kidney may cause glycosuria (renal diabetes) seems very probable (see p. 351).

The amount of urine is often enormously increased in diabetes, and as much as ten or fifteen litres may be passed in twenty-four hours. This is certainly dependent upon the abnormal quantity of sugar in the blood; for if, by proper methods, the latter be diminished, then the amount of urine also diminishes. Conversely, the greatest diuresis occurs in the cases with the largest amounts of sugar in the urine. The accumulation of dextrose in the blood or in certain tissues seems to produce an intense thirst, and the water that is taken for this causes the increase in the amount of urine. Yet no very absolute definite relation exists between the amount of urine, the excretion of sugar, and the feeling of thirst, and it has been shown, for example, that even though the same quantities of sugar are being excreted daily, the quantity of urine may be different in different patients.

Theory of Diabetes.—From the foregoing facts we shall now try to formulate a theory of diabetes mellitus. The sugar is excreted in the urine because of a hyperglycæmia, an excess of sugar in the blood. One cause of this excess in the blood is that the liver has lost, to some extent, the property of storing up the dextrose that comes to it either from the food or from the splitting up of proteids in the body. For those who believe that sugar can be formed in the body from proteids, the difference between a severe and a mild type of diabetes consists in

* Fichtner, Arch. f. klin. Med , vol. xlv p. 112.

the ability or inability on the part of the liver to store up, and on the part of the body to consume, the carbohydrates derived from proteid sources. For those who deny that sugar is normally formed out of proteids in the body, the essential feature of the severe form of diabetes is the formation of sugar in some abnormal manner from proteids. Pflüger's extreme view that sugar is never derived from proteids, unless these be glucosides, appears to me to be untenable; though it must be admitted that his views merit still further investigation.

It is impossible to say to what extent the glycogenic functions of other organs, such as the muscles, are impaired in diabetes. It seems certain, however, that in some way the pancreas assists the liver and muscles in their glycogenic function, and that this is one reason why lesions of the pancreas may lead to diabetes.

In the milder cases of diabetes, it is possible that no other disturbances of function are present than the above-mentioned impairment of the glycogenic functions in the body. In the more severe forms of diabetes, however, there is undoubtedly a diminution in the ability of certain cells of the body, perhaps the muscle-cells, to assimiliate sugar. The pancreas seems to assist in the assimilation of sugar in the body, possibly by furnishing an internal secretion that activates the glycolytic ferments in the muscles. This action of the pancreas is perhaps similar to that of the enterokinase of the intestines which converts a protrypsin into a trypsin, or to the intermediary body that plays such an important part in hæmolysis.

The glycogenic function of the liver may certainly be influenced through the nervous system, as is proved by the effects of experimental puncture of the fourth ventricle, and it is quite possible that the nervous system serves in some way to connect the liver and the muscles.[50] This influence of the nervous system upon the glycogenic function of the liver, would explain

* Pflüger, Pflüger's Arch., vol. xcvi. p. 1.

the etiological relation between nervous lesions and diabetes, a relationship that has been insisted upon by so many clinicians.

Finally, one can hardly help thinking that a diabetes may be caused by lesions of different organs, especially of the liver, the pancreas, the muscles, etc. Perhaps it will ultimately be possible to distinguish different forms of the disease according to their origin, but at the present time, the most experienced investigators in this field regard diabetes mellitus as an indivisible entity.

CHAPTER IX.

THE METABOLISM OF THE PURIN BODIES. GOUT.

THE nitrogen, derived from a certain class of proteids, the nucleo-proteids, is not excreted in the form of urea and ammonium salts to the same extent as is that derived from ordinary proteids. The characteristic constituents that enter into the composition of the nucleo-proteids are the nucleinic acids. When these undergo cleavage, they give rise to the purin or alloxuric bases, among which are adenine, guanine, xanthine, and hypoxanthine. A small portion of these bases appears in the urine as such, but the greater portion is eliminated in an oxidized form, as uric acid.[1] The uric acid and the purin bases are often spoken of together as the purin bodies.

Most of the uric acid that appears in the urine is derived in this manner from nucleo-proteids that are broken down in the body, or from purin bases or related compounds, such as caffeine or theobromine, that are taken in the food. Not all of the uric acid, however, is derived from these sources, for it is now practically certain that this acid may be formed synthetically in the human body, just as it is in the bodies of birds.[2] Nor does all of the nitrogen contained in the nucleinic acids appear in the urine as uric acid or related compounds, for a certain proportion is converted into urea in the body. This latter fact gives some basis to the old conception that uric acid represents an early stage in the formation of urea.

The quantity of purin bases in the urine serves therefore

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[1] Kossel, Ztft. f. physiol. Chem., vol. iii. p. 284; vol. vi. p. 422; Minkowski, Arch. f. exp. Path., vol. xxi. p 86; Horbaczewski, Monatsch. f. Chem., vol. xii. p. 221.

[2] See Wiener, Asher-Spiro, Ergebnisse, vol. i. p. 555; vol. ii. p. 377; Schmoll, Johns Hopkins Hosp. Bull., vol. xv. p. 377.

as a rough index of the bodily consumption of nucleo-proteids and purin bodies, derived either from the cellular metabolism or directly from the food.[3] Yet, as we have seen, it cannot serve as an accurate and absolute index of such consumption; for, on the one hand, not all of the nitrogen in the nucleinic acid appears in the urine as purin bodies, and, on the other hand, these bodies may be formed synthetically within the living organism.

Cell nuclei are very rich in nucleo-proteids; and when the food taken contains many nuclei, as is the case with thymus gland, for example, then the amount of purin bodies in the urine is greatly increased. Conversely, if a person avoids those substances which can be readily converted into purin bodies, such as the nucleo-proteids of meats and seeds, the caffeine of coffee, etc., then the quantity of uric acid in the urine is diminished, and that which does appear there represents the amount actually formed within the body. The amount of this " endogenous" uric acid has been found to be different in different individuals, though it is fairly constant for the same individual at different times.[4] It is apparently somewhat influenced by the ingestion of large quantities of non-nitrogenous food.[5]

The elimination of endogenous uric acid is increased whenever large numbers of cells, rich in nucleo-proteids, are being destroyed in the body. This was early demonstrated for a particular kind of cells, the leucocytes; and this fact, among others, led Horbaczewski to the belief that the leucocytes are a specific source for purin bodies, a view now proved to be incorrect.[6] Leucocytoses are, however, frequently accompanied

[3] Camerer, Ztft. f. Biol., vol. xxxv. p. 206; Weintraud, Kongr. f. in. Med., 1898, p. 190.

[4] Burian and Schur, Pflüger's Arch., vol. lxxx. p. 241; vol. lxxxvii. p. 239.

[5] Kaufmann and Mohr, Arch. f. klin. Med., vol. lxxiv. p. 141.

[6] See Hoffmann, Konstitutionskr.; Ebstein, Kongr. f. in. Med., 1889, p. 143.

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by an increased elimination of purin bodies, and when this is so, we may assume that an abnormal destruction of leucocytes is taking place in the body. Very large amounts of uric acid are often excreted in leukæmia, especially in the acute form of the disease.[7] In the chronic cases of this disease, the elimination of uric acid is usually increased, though in some no such increase in uric acid has been found.[8] Too little attention has been paid, however, to the excretion of the purin bases in these cases, for it has been shown that though the uric acid be normal, the purin bases, and consequently the total purin bodies, may be increased.[9]

The urine of the new-born child contains remarkably large quantities of uric acid. These are found at about the same time that uric acid infarcts are most liable to occur in the kidneys. The meaning of this increased elimination, however, is not yet fully understood.[10]

Gout.—Gout is characterized by the deposition of monosodium urate crystals in various parts of the body, especially in the hyaline and fibrous cartilages, in the tendons, in the subcutaneous and intermuscular connective tissues, and in the kidneys. These deposits take the form of clusters of needle-like crystals. No symptoms may be caused by such a deposition of urates, especially when it takes place gradually and in certain localities, as the subcutaneous tissues and some cartilages. These urate deposits, known as tophi, often attain a large size, and they may then break through the skin or again disappear without having caused any unpleasant sensations. In these cases it seems improbable that the uric acid should have been formed locally by the cells, for the strands of con-

[7] Magnus-Levy, Virch. Arch., vol. clii. p. 107.

[8] Gumprecht, Ztrbl. f. Path. vol. vii. p. 824.

[9] Gottlieb and Bondzynski, Arch. f. exp. Path., vol. xxxvi. p. 127: Gumprecht, loc. cit.

[10] Sjöquist, cit. Jahresber. f. Thierche, vol. xxiii. p. 245.

nective tissue are pushed aside, and the tophi increase in size by new deposits on their exteriors.

On the other hand, the deposition of urates in the tissues may lead to a more or less marked inflammatory reaction in the neighborhood, and this may be accompanied by the characteristic paroxysm of acute gout. Suddenly or after some prodromal symptoms, the patient is awakened at night by violent pains in one or more joints, usually in the metatarsophalangeal joints of the great toes. The affected joint and the neighboring tissues become intensely inflamed, and the skin over them becomes œdematous. These very acute symptoms usually do not last long, and after a few hours or days they all disappear without necessarily leaving any alterations in the joint that can be demonstrated even by anatomical methods. These typical acute gouty paroysms may recur at varying intervals; but gradually they become less and less characteristic, the patient becomes cachectic, and the " regular gout" is said to have become transformed into the asthenic form of the disease.

The exact cause of these typical paroxysms is uncertain. According to one view, the inflammation is caused by the deposition of uric acid or some of its derivatives in the tissues. At present, however, this is a pure hypothesis, unsupported by facts, and it encounters the great objection that tophi are frequently formed without any symptoms whatever. According to another view, the paroxysms are caused by a too rapid solution of urates from old deposits, yet this view likewise lacks the support of direct evidence. In truth, no satisfactory explanation of the gouty paroxysms can be given, and we are equally ignorant concerning the nature of many associated gouty manifestations, such as the granular kidney and the heart changes, the pulmonary, nervous, and ocular complications and the general cachexia.

It is said that a tendency to gout may be inherited, and that

the disease may be caused by excesses in food and drink. We consider, however, that caution is necessary in the acceptance of these views, for they rest not upon convincing statistics, but rather upon so-called clinical experience and impressions. More accurate data on this subject are therefore very desirable. That chronic lead poisoning favors the development of gout can hardly be doubted,[11] though how it does so is quite uncertain. The nature of the relation between gout and diabetes mellitus and between gout and obesity are likewise unsolved.

Uric Acid in the Blood during Gout.—During the gouty paroxysm, uric acid crystallizes out of the blood with abnormal ease after the addition of acetic acid.[12] It crystallizes out of normal blood in a similar manner only when a large amount of nuclein compounds have been taken in the food. In pathological conditions other than gout, especially in leukæmia, however, large quantities of uric acid will at times crystallize out of the blood just as it does in acute gout.[13] In the intervals between the gouty paroxysms no such excess of uric acid in the blood can be demonstrated.

It is impossible to explain the ease with which uric acid precipitates out of gouty blood, so long as we do not know how it is held in solution in normal blood.[14] To dissolve one part of uric acid about thirty-eight thousand parts of pure water are necessary,[15] yet serum will dissolve uric acid at the body temperature up to a concentration of about 0.18 per

[11] Lüthje, Ztft. f. klin. Med., vol. xxix. p. 266.

[12] Garrod, The Nature and Treatment of Gout; Klemperer, Deut. med. Wochens., 1895, No. 40; Magnus-Levy, Ztft. f. klin. Med., vol. xxxvi. p. 366.

[13] Magnus-Levy, Virch. Arch., vol. clii. p. 107; Ztft. f. klin. Med., vol. xxxvi. p. 372.

[14] See Minkowski, Gicht in the Nothnagel System; G. Klemperer, Kongr. f. in. Med., 1902, p. 219; Goto, Ztft. f. physiol. Chem., vol. xxx. p. 473.

[15] His and Paul, Ztft. f. physiol. Chem., vol. xxxi. pp. 1 and 64.

cent.[16]   Minkowski has called attention to the fact that too great stress is ordinarily laid upon the alkali of the blood as a solvent for uric acid, and too little attention has been paid to the possibility that the acid is held in solution in some other combination, such as one with nucleinic acid.

The increased amount of uric acid in the blood of gouty patients can hardly be regarded as the sole cause of the precipitation of the mono-urate in the tissues, for the blood contains excessive amounts of uric acid in other conditions, such as leukæmia, for example.   Furthermore, there is no reason to suppose that the blood of gouty patients cannot dissolve as much acid as does the blood of normal individuals.   At least, no diminution in the alkalinity of the blood can be demonstrated, either by determinations of the carbon dioxide dissolved or by direct titrations.[17]   Klemperer has shown, indeed, that the blood of these patients is still capable of dissolving even considerable amounts of uric acid.

The Uric Acid in the Urine in Gout.—Previous to the gouty paroxysms, there is a diminished excretion of uric acid in the urine; whereas, during and just after the paroxysm, more is excreted than at other times.[18]   The excretion of the purin bases is also said to be increased along with the increase in uric acid.   If food rich in nuclein compounds—e.g., thymus —be taken during the paroxysm, the uric acid is not excreted so well as it is by a normal individual.[19]

In chronic gout, and during the intervals between the paroxysms of acute gout, no definite abnormalities in the excretion of uric acid can be demonstrated,[20] although Soetbeer believes

[16] G. Klemperer, Deut. med Wochens , 1895, No. 40.

[17] Magnus-Levy, Ztft. f. klin Med., vol. xxxvi. p 376.

[18] His, Arch. f. klin. Med., vol. lxv. p. 156; Magnus-Levy, Ztft. f. klin. Med., vol. xxxvi. p. 380.

[19] Vogt, Arch. f. klin. Med., vol. lxxi. p. 21; Soetbeer, Ztft. f. physiol. Chem , vol. xl p 25

[20] His, Arch. f. klin. Med., vol. lxv. p. 156.

that after the administration of meat the excretion of uric acid did not follow precisely the normal course, and in some cases it was quantitatively diminished or delayed.[21]

One might be inclined to attribute the increase of uric acid in gouty blood to an insufficient excretion of urates by the kidneys, and this supposition receives some support from the fact that other nitrogenous waste products may also be retained in the body, both in the acute paroxysms and in chronic gout.[22] No anatomical grounds for such a retention are, however, demonstrable, for the gouty granular kidney is usually only a late manifestation of the disease.

The retention of uric acid in gout may not be due to renal changes at all, and Minkowski's idea that this substance circulates in a form which is not readily excreted is deserving of careful investigation. That some such relation may exist is supported by the fact that a retention of ammonium and potassium salts has been observed during the gouty paroxysm.[23]

The Cause of the Local Deposits of Urates.—According to many of the best observers,[24] the local deposit of the urates in gout is caused by changes in the cells of the affected regions. This seems to be true in the primary attacks at least. As has been mentioned, however, there is less reason to believe that the more chronic deposits in the subcutaneous tissues, etc., are caused by primary cellular changes. Ebstein has laid great weight upon a primary necrosis of the tissue as the cause of the precipitation of urates, but later researches have not supported his views.[25]

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[21] Ztft. f. physiol. Chem., vol. xl. pp. 25, 55.

[22] Vogel, Ztft. u. klin. Med., vol. xxiv. p. 512; Schmoll, Ztft. f. klin. Med., vol. xxix. p. 510; Magnus-Levy, Ztft. f. klin. Med., vol. xxxvi. p. 380; Vogt, Arch. f. klin. Med., vol. lxxi. p. 21.

[23] Soetbeer, Ztft. f. phys. Chem., vol. xl. p. 55.

[24] Klemperer, Horbaczewski, v. Noorden.

[25] Freudweiler and His, Arch. f. klin. Med., vol. lxiii. p. 266; His, ibid., vol. lxvii. p. 81.

Theory of Gout.—It must be admitted that, in the present state of our knowledge, no adequate theory to explain gout has been advanced and that we hardly know more than that it is associated in some way with a perversion of the uric acid metabolism. To attain to a more satisfactory knowledge of this subject, it will be necessary to arrive at some more definite understanding as to the relation which exists between the formation and the excretion of uric acid under normal as well as pathological conditions, to obtain more accurate data as to the amount of uric acid contained in the tissues and fluids of the body, and, finally, to know the form in which uric acid is normally held in solution. The latter is, perhaps, of primary importance, and definite disturbances in the solubility of the uric acid would explain many facts connected with gout.

CHAPTER X.

FEVER.

FEVER is characterized by an increase in the temperature of the body and by certain changes in the metabolic processes.[1] The temperature in fever is higher than is normal for the time of day at which it is taken. The temperature is furthermore much less constant than is the normal temperature, and the considerable variations that it undergoes are due partly to external influences and are partly spontaneous, or, at least, due to causes which escape our methods of observation.

As a rule, the diurnal variations of the temperature in fever are of the same character as those which take place in health,— *i.e.*, there is an elevation toward evening and a fall toward morning. Those who work at night and sleep during the day show at times the inverse type of diurnal variation both in health and fever. Thus we see that the same causes, such as food, light, work, etc., which influence the temperature curve of healthy persons, also influence the variations in the temperature of fever patients. In many fevers, however, the variations in temperature are quite irregular, or they follow some special type that is characteristic of the disease.

The rise of temperature is only one of a number of phenomena which are present in fever, and it is often difficult to decide whether many of the other symptoms are to be ascribed to the high temperature or are due directly to the agent that causes the fever. We only are justified in regarding a particular symptom as a result of the increased temperature when it is found to occur in all forms of fever, no matter how they are caused.

[1] See Krehl, Kongr. f. in. Med., 1898, p. 229.

The Normal Regulation of the Body Temperature.—The temperature of man is maintained at an almost constant level under the most varying conditions; indeed, it varies less than that of any other animal. We shall therefore first consider the mechanism by which the temperature is normally maintained at this uniform level.[2]

If large quantities of heat are suddenly set free in the body from any cause, such as muscular work or the ingestion of large amounts of food, then the total loss of heat from the body is correspondingly increased. The cutaneous vessels dilate and the warmer skin loses heat more rapidly by radiation and conduction. The affected person perspires more freely, and the loss of heat by evaporation of water from the skin is likewise increased. Whether the one or the other of these various means for eliminating heat is utilized to a greater or less extent in the individual case depends upon a variety of conditions, which cannot be considered in this place.

If, on the other hand, a warm-blooded animal is exposed to cold, it is able to protect itself from considerable losses of heat, which would otherwise tend to reduce its temperatures. The skin vessels contract and the heat losses through conduction and radiation are diminished. Men ordinarily wear thicker clothes under these circumstances, and so surround their bodies with a layer of comparatively warm air. By these means it is possible to maintain the normal bodily temperature, even when the individual is exposed to considerable degrees of cold. If, however, this mechanism is insufficient to meet the emergency, then a new factor is called into play. The production of heat in the body is increased, the seat of this increased production being the muscles, according to the best authorities.

When a man is exposed to cold, therefore, the first regu-

[2] See Rubner's classical work, Die Gesetze des Energieverbrauchs bei der Ernahrung, Leipzig, 1902.

latory mechanism that serves to maintain his body temperature at the normal level is of a physical character; *i.e.*, losses of heat are prevented. As we have just seen, however, this means of regulation may be insufficient, and the exposure to cold is then followed by an increased production of heat in the body. The individual feels chilly and shivers, and thereby increases the combustion in his body, and, even though no gross muscular movements occur, the body metabolism may yet be increased, as has been proved by recent experiments. In such a case the extra heat is generated mainly by the combustion of non-nitrogenous material, just as it is when heat originates from muscular activity. This regulation of the body temperature by variations in the heat production is termed a chemical regulation in contradistinction to that which depends upon variations in the heat losses, the so-called physical regulation.

The point at which the chemical mechanism steps in to maintain the temperature of the body depends in part upon the degree to which the animal is able to limit his loss of heat and in part upon the amount of food which has been taken. The heat that is immediately set free when food is taken would ordinarily be quickly disposed of by an increased elimination of heat; but if the body is exposed to cold, this extra heat serves to maintain the body temperature. It thus obviates the necessity of calling the chemical regulation into play.

These are, in brief, the means whereby the healthy man regulates his bodily temperature under varying external and internal conditions. Under certain circumstances, however, even the normal mechanism is insufficient to keep the body at a constant temperature. For example, if heat be applied to the surface of the body, and if, at the same time, the compensatory loss of heat be interfered with, then a rise in temperature necessarily follows. For this reason, every man becomes warmer in a steam bath, or in a warm-water bath of 40° C.

(104° F.) or over. Possibly, however, some become warmer than others under the same conditions.

An increased production of heat within the body by excessive chemical decomposition may also cause a rise in temperature, and this happens more frequently than is generally supposed.[3] Muscular exertion, even if not very severe, may thus raise the temperature of the body. In this respect, different individuals certainly react differently, and the novice becomes overheated in doing a certain piece of work more easily than does the adept, mainly because he uses more energy to accomplish the same result. Another factor that is of great importance here is the ease with which heat may be eliminated from the body. This explains many of the apparent contradictions met with in literature concerning the effect of muscular exertion upon the body temperature. The man that makes the ascent of Monte Rosa does not become warmer from the great exertion, because the low temperature and the dryness of the surrounding air greatly favor the loss of heat from his skin and lungs.[4] On the other hand, the temperatures of soldiers frequently rise during forced marches, for they are heavily dressed and they must often travel in a warm, moist climate.

Heat Stroke.—If the temperature of the body becomes considerably elevated from such outside causes, we speak of it as a heat stroke.[5] The temperature under these conditions may reach 43° C. (110° F.) or over, the pulse becomes rapid, the patient becomes dizzy or delirious, and in severe cases coma and death terminate the scene. The high temperature often persists in these patients for hours, or even days, after the

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[3] Hiller, Ztft. f. klin. Med., vol. xxiii. p. 399; Wolpert, Arch. f. Hyg., vol. xxvi. p. 32.

[4] Calberla, Arch. f. Heilkunde, vol. xvi. p. 276; Bonnal, Comptes rendus, vol. xci. p. 798.

[5] Zuntz, Berl. klin. Wochens., 1896, No. 32.

actual cause of the stroke is over.   This would seem to indicate some injury to the heat-regulatory mechanism.   Heat-stroke patients are often described as being pale, livid, or cyanotic, which conditions indicate an improper peripheral circulation and a consequent improper regulation of the heat losses from the surface of the body   This poor peripheral circulation is apparently due to an injury to the regulating centres in the brain, though the nature of this injury is not known.

The experience of military surgeons has taught us that excessive heat is most liable to affect those who are in some way indisposed, who are foot-sore, or who are convalescent from severe illness, and it has frequently been observed clinically that persons who are ill, particularly anæmic or tuberculous patients, are especially prone to show a rise of temperature after exercise, or even after meals.[6]

It may be questioned whether the rise of temperature produced by such external agencies should be regarded as fever or not.   One might say that the heat regulation is sufficient under ordinary circumstances, but insufficient when special demands are made upon it   Such a distinction is merely one of degree, and the comparison could then be made with the heart which is sufficient so long as the body is at rest, but becomes insufficient when increased work is demanded of it.

It were perhaps better to attempt to draw a line dividing those cases in which regulatory mechanism is affected, as it is known to be in fever, from those in which the regulatory mechanism is normal, but cannot reduce the temperature owing to the nature of the conditions that surround the body.

In heat stroke the conditions are very complicated, and the rise of temperature is not due to external forces alone.   Other factors, in addition, are certainly present, for different indi-

[6] Penzoldt and Birgelen, Münch. med. Wochens., 1899, Nos. 15, 16, 17; Ott, ibid., 1901, No. 50, and 1902, No. 38; Schröder and Brühl, ibid., Nos. 33, 34, and 45.

viduals show considerable differences in their susceptibility to changes in their environment. Some lose heat more readily than others, a fact that is especially true of thin individuals as compared with stout ones. Heart lesions render a patient very susceptible to heat stroke, for a good peripheral circulation is a necessity when the losses of the heat from the body must be increased.[7] (An overindulgence in alcohol also renders an individual more susceptible to heat stroke. Finally, those who have had once a sun stroke may manifest for years a markedly increased susceptibility to changes in the temperature about them.—ED.) All these facts demonstrate that changes in the external conditions are not the sole factors which produce the sun stroke. The mechanism for losing heat is certainly less efficient in some individuals than in others, and in so far as the heat stroke depends upon an insufficiency of heat elimination it bears a certain resemblance to true fever.

Heat Regulation in Fever.—The cause of the high temperature of fever must be some disproportion between the production and the loss of heat in the body. Theoretically, fever might be caused either by an excessive heat production without a corresponding increase in the heat loss, or by a diminution in the heat loss without a corresponding diminution in the heat production. We now propose to consider which of these conditions actually exists in fever, and whether or not all cases of fever are produced in the same manner.

Two general methods have been employed to determine the amount of heat produced in the body. In the first, the amount of heat lost has been directly measured in a calorimeter (direct calorimetry). In the second, the products of combustion have been determined and the heat produced calculated (indirect calorimetry). The two methods have been shown to yield identical results in the healthy ·animal,[8] and

[7] Thurn, Deut. militärärztl. Ztft., 1895, p. 289.
[8] Rubner, Ztft. f. Biol. N. F., vol. xii. p. 73.

we have every reason to believe that the results would also be the same in fever, although this has not yet been definitely proved, on account of technical difficulties.[9]

Heat Production in Fever.—In the vast majority of all fevers the production of heat is increased. This has been proved for different diseases of man, such as pneumonia, typhoid fever, pleurisy, erysipelas, tuberculin fever, etc.,[10] as well as for various septic diseases of animals,[11] and for fevers produced experimentally by injections of bacteria and various chemical substances.[12]

This increase in heat production is quite marked at the time when the temperature is rising and at the height of the fever. It is greatest of all during the chill which initiates so many infections, obviously on account of the violent muscular contractions that take place at that time. During the height of the fever, it is found to be the most marked in those who breathe violently, from whatever cause; here also because of the excessive muscular exertion. If we eliminate these cases, in which the heat production is accelerated by muscular activity, then the increased production of heat in fever usually amounts to from ten to sixty per cent., the average being about twenty to thirty per cent.

In a small number of cases no apparent increase of heat production above the normal limits can be demonstrated.[13] Such observations have been made, for the most part, upon patients in whom there was but little fever or in whom the

[9] See Krehl and Matthes, Arch. f. exp. Path., vol. xxxvii. p. 284.

[10] Leyden, Arch. f. klin. med., vol. vii. p. 536; Liebermeister, ibid., vol. viii. p. 153; Loewy, Virch. Arch., vol. cxxvi. p. 218; Riethus, Arch. f. exp. Path., vol. xliv. p. 239.

[11] Leyden and Fraenkel, Virch. Arch., vol. lxxvi. p. 136.

[12] Krehl and Matthes, Arch. f. exp. Path., vol. xxxviii. p. 284.

[13] F. Kraus, Ztft. f. klin. Med., vol. xviii. p. 160; Kraus and Chvostek, Wiener klin. Wochens., 1891, Nos. 6 and 7; Loewy, Virch. Arch., vol. cxxvi. p. 218; Krehl and Matthes, Arch. f. exp. Path., vol. xxxviii. p. 284.

fever was long continued. In the latter class of cases it is necessary to remember that the organism tends to limit its metabolism in long-continued illnesses, so that although the quantity of oxygen consumed by these patients with fever may not have exceeded the normal limits, it was in reality above what would have been consumed had no fever been present. For accurate comparisons in such cases, comparative determinations should be made upon the same individual during periods of fever and of apyrexia.

In still another class of cases high fever may be associated with an unusually low production of heat—viz., when there is a tendency to collapse. As we shall see later, a diminution in the heat production is one of the characteristics of collapse, and even when a tendency to this condition is present the heat production may be lessened.

In a final group of cases no reason can be given for the slight production of heat, and in these it is possible that the sole cause of the rise of temperature is a limitation of the heat losses from the body.[14]

Thus we see that in the great majority of all cases of fever, and especially in fevers of short duration, the production of heat in the body is increased. This increase is most marked at the beginning of acute infectious diseases, whereas, in chronic wasting diseases the heat production tends to become limited, and when the temperature is falling it may even be less than normal.

As we have said, the average increase in the heat production in fever is about 20 to 30 per cent. Such an increase is not extraordinary when we remember that Rubner was able to increase the heat production in dogs sixty per cent. solely by feeding them with large quantities of proteid food, and that in severe muscular exertion the heat production may be several times as great as during rest. Normally, the body

[14] Rosenthal, Berl. klin. Wochens., 1891, No. 32.

can dispose of much larger amounts of heat than are liberated within it during fever, so that the cause of the high temperature in fever cannot be an increased production of heat alone.

Indeed, a portion of the increase in heat production is due to the elevation of the body temperature itself, for we know that oxidative processes in general are accelerated by heat, and Pflüger has estimated that for every increase of 1° C. in a rabbit's temperature, its heat production increases about six per cent., and the same has been shown to be true when the temperature of man is artificially elevated.[15] Thus we see that an increase of heat production, amounting to about twelve to eighteen per cent. of the normal, might easily be explained as an effect rather than as a cause of the increased bodily temperature. The excessive heat production in fever, therefore, may be explained in part as a result of increased muscular movements and in part as the result of the higher temperature of the body. The remaining increase in heat production is very slight; especially if it be compared to that which results from violent exercise or from the ingestion of large quantities of proteid food.

The Loss of Heat at the Beginning of Fever.—During the rise of temperature the loss of heat from the body is almost always found to be diminished, the losses by radiation and conduction from the skin being especially limited. The amount lost by evaporation of water is frequently increased, however; for, even at this period, the metabolic processes in the body may be accelerated. Yet the increased loss by evaporation does not neutralize the decrease in loss by conduction and radiation, and frequently, furthermore, the loss of water is also less than normal. Thus at the onset of fever the animal utilizes all of the means at its disposal to raise its temperature. The production of heat is increased and the losses are diminished.

[15] Linser and Schmidt, Arch. f. klin. Med., vol. lxxix. p. 514.

The loss of heat from the surface of the body is regulated mainly by the contraction of the cutaneous blood-vessels. At the onset of many diseases these vessels contract excessively, and, as a consequence, the skin becomes cold and either pale or cyanotic. This cooling of the skin produces in turn a sensation of cold throughout the body and sets in motion the chemical mechanism already referred to (p. 378), which increases the heat production within the body. Clonic muscular movements, giving rise to the so-called chill, are a consequence. During the chill, the temperature rises rapidly to a great height, for the muscular movements greatly increase the heat production, and, at the same time, the heat losses are reduced on account of the contracted cutaneous arteries. That these muscular contractions are due primarily to the coolness of the skin is proved by the fact that, if the skin of these patients be warmed, the "chill" ceases Such chills are particularly characteristic of some diseases. and it seems probable that the agents which cause certain fevers show a special tendency to produce a constriction of the cutaneous vessels, and consequently a chill.

The Heat Loss at the Height of the Fever.—In the great majority of cases the total loss of heat is increased at the height of the fever. This is necessarily true when the heat production is increased and the temperature is constant, for it is obvious that, if the extra heat produced were not immediately given off, the temperature of the body would be raised.

In animals the acceleration in heat losses affects conduction, radiation, and evaporation, all to about the same degree; so that the ratio between the first two and the third remains practically the same as in health,—*i e.*, the loss by the evaporation amounts to about sixteen to seventeen per cent. of the total loss of heat.[16] In my opinion, however, we are not permitted

[16] Nebelthau, Ztft. f. Biol, vol xxxi. p. 293; Krehl and Matthes, Arch f exp Path, vol xxxviii. p. 284.

to infer from this that sufficient evaporation from the body takes place in fever, for it has been shown that, if the heat production be increased by other means, the losses by evaporation are relatively much more increased than are the losses by radiation and conduction.[17]

Lang has studied these relations in man.[18] In his experiments he showed that the ingestion of food greatly increased the evaporation of water from the bodies of both healthy and feverish patients; and that, on the other hand, if the patient were fasting, the evaporation from the skin during the rise of fever was less than the normal, and during the height of the fever it was approximately the same as normal. The loss of water by way of the lungs, however, was considerably increased, owing to the larger amount of air breathed. His results, therefore, would seem to indicate that although the excessive heat derived from food will increase the evaporation from the skin even in fever patients, the excessive heat caused by the fever itself does not tend to increase this evaporation. As yet, however, we cannot regard the question concerning the loss of heat by evaporation during fever as being definitely settled, for Lang's experiments were only of short duration. Nevertheless, it seems very probable that the cause of the rise of temperature in fever is, in part at least, an insufficient evaporation of water from the skin.[19]

Though the total heat loss during the height of the fever is ordinarily greater than normal, it is probably not so in those chronic cases already referred to, in which the heat production is normal or even diminished (p. 382); for, as we have said, so long as the temperature of the body remains constant, the total heat loss must equal the total heat production. It is only

[17] Rubner, Arch. f. Hyg., vol. xi. p. 256; Wolpert, ibid., vol. xxvi. pp. 32, 68; Zuntz, Berl. klin. Wochens., 1896, No. 32.

[18] Arch. f. klin. Med., vol. lxxix. p. 343.

[19] See also Leyden, Arch. f. klin. Med., vol. v. p. 273.

during a rise or fall in the body temperature that the one exceeds the other.

The conduction and radiation of heat from the skin are mainly governed by the amount of blood that traverses the cutaneous capilaries, and, since the latter are usually dilated at the height of the fever, the skin is ordinarily reddened at this time. Yet many questions concerning the cutaneous vessels in fever are still unsolved. They certainly respond excessively to stimulation, either mechanical or thermic, and, for this reason, fever patients easily become chilled when exposed to a draught of air, etc. Animals with fever also react excessively to reflexes which affect the cutaneous vessels through the medulla.[20]

Many have held that the cutaneous vessels of fever patients are subject to frequent and rapid variations in their state of contraction. This is certainly not always so, however, for, though recent and careful observations on animals have shown that during the rise of temperature considerable variations in the heat loss may take place, the same is by no means true during the height of the fever.[21] Furthermore, there are no very marked variations in the skin temperature of man during typhoid fever, rheumatic endocarditis, and many other conditions.[22]

Despite our inadequate knowledge on many of these points, we may say in conclusion that the temperature remains elevated during the height of fever, mainly because the mechanism regulating heat loss is ineffectual, and especially because the evaporation of water from the skin is insufficient. It seems as if the manner in which heat is produced during fever does not furnish an adequate stimulus to the mechanism that increases the loss of heat from the body, for if the heat pro-

[20] Heidenhain, Pflüger's Arch., vol iii p. 504, vol. v. p. 106.
[21] Nebelthau, loc. cit.; Krehl and Matthes, loc. cit.
[22] Grunenwald, Arch. f. klin. Med., vol. lxxviii. p. 333.

duction of fever patients be increased in some other manner, as by the taking of food, for example, the extra heat thus produced increases the heat elimination.[23]

The Heat Loss during the Fall of Temperature.—This differs under different conditions. When the fall of temperature takes place rapidly by crisis, the loss of heat is greatly increased by the sweating and by the increased radiation and conduction from the skin. When the fall of temperature takes place very gradually, however, the heat loss is often very slight. In such cases the fall is due mainly to a diminished heat production, as has been definitely proved for animals, and as is probably equally true of man. In the majority of cases, however, the fall of temperature seems to be due to a combination of diminished heat production and increased heat loss.

Quantitative Metabolic Changes during Fever.—During the rise of temperature, as well as during the height of fever, the oxidative processes in the body are usually increased. They run parallel to the heat production, and, indeed, may be used to measure heat production (indirect calorimetry), providing that we know what compounds are being oxidized and what the end products are. Chills and rapid respirations—*i.e.*, muscular activity—greatly accelerate the metabolism, and a high temperature will do the same. In some cases of fever, however, there is no apparent increase in the metabolic process (p. 382). No strict parallelism exists between the rate of decomposition and the elevation of temperature,[24] and many infections run their course with comparatively slight fever and yet with comparatively rapid rates of oxidation.

The Proteid Metabolism during Fever.—Since most fever patients are placed upon an insufficient diet, their metabolism must be compared with that of healthy individuals who are on an equally low diet. It has been shown that during fever

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[23] Lang, Arch. f. klin. Med., vol. lxxix. p. 343.

[24] See Riethus, Arch. f. exp. Path., vol. xliv. p. 247.

there is an increased consumption of proteid material, both in men [25] and in animals,[26] though some few observers have failed to confirm these findings.[27] In many cases the increased proteid destruction begins even before the rise of temperature,[28] and when the temperature falls rapidly, the increased elimination of nitrogenous waste products frequently continues for some days after the temperature has become normal (the " epicritical excretion of urea").[29] Fever is, therefore, one of the conditions that injure the proteids of the body and increase nitrogenous metabolism.

The rapidity of proteid decomposition varies greatly in different infections and in different individuals. It is most rapid in acute processes and in young, strong persons, and it is often comparatively slow in chronic wasting diseases. It bears no definite fixed ratio to the degree of temperature.

The proteid decomposition in fever follows other lines than are followed during health, whether the individual is fasting or not. The significance of the appearance of aceton bodies in the urine need not be discussed here, for they are caused, in part at least, by the inanition, and it is questionable whether they are derived from the decomposition of proteids or of fats. It is certain, however, that a hydration of the proteid molecules occurs in fever, for albumoses mostly of the deutero group, have been found very frequently in the urine.[30] To what extent this cleavage of the proteids is characteristic of fever will be discussed in another place (p. 390).

Most of the end products of proteid decomposition that

[25] See v. Noorden, Path. d. Stoffwechsels, p. 193.

[26] Krehl and Matthes, Arch. f. exp. Path , vol. xl. p 396.

[27] Pipping, Skandinav Arch. f physiol , vol. ii. p. 89.

[28] Ringer, Trans. of the Med and Chir. Society, vol. xlii. p. 361 ; May, Ztft. f. Biol., vol. xxx. p. 1.

[29] Naunyn, Arch. f. exp. Path , vol. xviii p 49.

[30] Schultess, Arch. f. klin. Med , vol. lviii p. 325 ; vol lx p. 55 ; Krehl and Matthes, ibid., vol. lx. p. 501.

appear in the urine do not differ from those present in health.[31] The urea is relatively reduced and the ammonium salts of organic acids increased.[32] The increase in the amount of these organic acids in the blood is the probable cause of the diminution in the amount of carbon dioxide that is present there.[33] As a rule, the creatinin is also increased in the urine. We have no positive information as to the amount of uric acid formed during fever.

The excessive proteid decomposition in fever is caused in part by the elevation of temperature.[34] If a fasting animal be heated, the proteid decomposition is always increased, though if it is taking large amounts of food, this increase is little or not at all greater than would be the increase in the nitrogenous metabolism of normal animals under the same conditions. So far as man is concerned, it has also been shown that if the temperature is artificially raised as high as 39° C., the proteid decomposition is not greatly affected; whereas, if the temperature reaches 40° C. or over, an increase in proteid decomposition always takes place.[35]

On the other hand, it is certain that the increased proteid destruction during fever is caused only in part by the elevation of temperature, for in fever this destruction is considerably greater than it is in artificial overheating of the body. This extra proteid decomposition may be due in part to the inanition, but it is especially due to the direct action of the toxic agent that causes the fever. In this respect it resembles the excessive nitrogenous metabolism present in certain cases of carcinoma, etc.

[31] Bohland, Pflüger's Arch., vol. xliii. p. 30; Gumlich, Ztft. f. phys. Chem., vol. xvii. p. 10.

[32] Bohland, loc. cit.

[33] See G. Klemperer, Kongr. f. in. Med., 1890, p. 391.

[34] The observations to the contrary have been explained by F. Voit, Sitzungsber. d. Ges. f. Morph. u. Physiol. in München, 1895, Heft II.

[35] Linser and Schmid, Arch. f. klin. Med., vol. lxxix. p. 514.

This hypothesis—that the excessive proteid decomposition in fever is largely due to toxic influences—is supported by the fact that no success has hitherto attended the attempts to cause the proteid metabolism in fever to follow the same lines as it does in health. These excessive decompositions may, indeed, be lessened by the administration of large quantities of carbohydrates and fats,[36] but not to the same extent as it is in the normal individual.[37]

The Non-Nitrogenous Metabolism during Fever.—It is uncertain to what extent the non-nitrogenous constituents of the proteid molecules are consumed in fever. The increased heat production might all be accounted for, if we assume that the affected proteids are completely burned.[38] If this were the case, then there should be no consumption of the fat or of the glycogen in the body. Yet we know, as a matter of fact, that glycogen is rapidly consumed in fever, and that patients with fever do not seem able to lay up any great store of this carbohydrate.[39] It would be interesting to determine quantitatively the total heat production and the total glycogen of the body in fever, and so to discover if there is a retention in the body of some non-nitrogenous constituents of the proteid molecules, possibly as fat.

The respiratory quotient in fever may not differ from the normal quotient,[40] yet in many infectious processes, as in erysipelas, typhoid fever, pneumonia, etc., it has frequently been found to be abnormally low.[41] This low respiratory

[36] Weber, Arch. f. exp. Path., vol. xlvii. p. 19.

[37] For the opposing view, see Hirschfeld, Berl. klin. Wochens., 1891, Nos. 2 and 8; May, Ztft. f. Biol., vol. xxx. p. 1.

[38] Senator, Untersuchhungen uber d. fieberhaften Prozess, Berlin, 1873; Kraus, Ztft. f. klin. Med., vol. xviii. p. 160; May, loc. cit.

[39] Hirsch and Rolly, Arch. f. klin Med., vol. lxxv. p. 307; Rolly, ibid., vol. lxxviii. p. 248; Ott, ibid., vol. lxxi. p. 263.

[40] F. Kraus, Ztft. f. klin Med., vol. xviii p. 160.

[41] Regnard, Resherches sur les combustions respiratoires; Riethus, Arch. f exp. Path., vol. xliv. p. 254.

quotient depends not upon the temperature itself, but upon the cause of the fever, for it has been also found during the afebrile periods of an intermittent fever. There is no reason to believe that it depends upon an increased elimination of the carbon dioxide by other channels than the lungs, as by the skin or the urine.[42] This low respiratory quotient would therefore seem to indicate the retention in the body of some compound rich in carbon and oxygen.

Diabetic patients frequently eliminate no sugar in their urine during fever; but we need further observations on this point in order to be certain that this is not an effect of the altered diet. In some cases the elimination of sugar has been found to be greater during fever than during health, and some believe that this is even the rule in diabetes.[43] It is well known that alimentary glycosuria may be induced with unusual ease in fever patients, thus showing that their tolerance for sugar is diminished.[44] Dogs from which the pancreases have been removed do not show any uniform variations in their carbohydrate metabolism during fever.[45]

So far as we know, no changes in fat metabolism occur during fever. It is apparently carried on precisely as in any other condition of under-nutrition.

The Cause of the High Temperature in Fever.—We have already said that a rise in temperature must always be due to a disproportion between the heat production and the heat loss in the body. Since the production of heat in fever is greater than in health, it is theoretically possible that this increased production of heat may be the sole cause of the high temperature. Yet we know that much larger amounts of heat

[42] Scholtz, Arch. f. exp. Path., vol. xl. p. 326.
[43] Mohr, Ztft. f. klin. Med., vol. xlii. p. 402.
[44] De Campagnolle, Arch. f. klin. Med., vol. lx. p. 209; Strauss, Ztft. f. klin. Med., vol. xxxix. p. 202.
[45] Nebelthau, Arch. f. exp. Path., vol. xlvi. p. 385.

may be produced in the normal individual by muscular exertion and by a large proteid meal, and that these do not ordinarily cause any marked rise in temperature. It seems probable, therefore, that in fever the fault lies in the mechanism which regulates the heat loss, and we have already expressed the view that, for some reason, the heat in fever is produced in such a manner that it does not furnish the normal stimulus to the mechanism that increases heat loss. Yet so long as we are ignorant as to the nature of the stimuli that normally increase the loss of heat from the body, it seems unprofitable to discuss the pathological changes which these stimuli may undergo.

The Site of the Heat Production in Fever.—The character of the metabolic changes in fever give us no definite idea as to the tissues especially affected, for the appearance of such abnormal products as the albumoses and oxyacids in the urine signify nothing more than that the destruction of the cellular constituents of the body is increased. The evidence in favor of an increased consumption of red blood-corpuscles is very inconclusive. Neither the increased amounts of potassium salts in the urine nor the abnormal pigments there present can be considered to prove a wide-spread destruction of these elements, and the blood picture itself is directly opposed to such an assumption.

Observations on the temperature of the blood returning from various parts of the body do, however, give us some data as to the site of the heat production. Heidenhain and Körner[46] found that when artificial fever had been produced in dogs by the injection of pus, the blood returning from the legs was warmer than that in the right ventricle. Numerous other observers have since shown that, in artificial fever, the venous blood returning from the kidneys, and especially from

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[46] Pfluger's Arch., vol iii. p. 562.

the liver, is warmer than that from the muscles and the skin.[47] From these observations, we may infer that the excessive heat of fever is produced mainly in the large glands and the muscles, but to what extent each of these participates in its production is very uncertain.

Since the glycogen of the body is consumed during fever, and since the same occurs when artificial fever is produced by puncture of the brain,[48] it would seem possible that the cause of the increased heat production in ordinary fever is a stimulation of the central nervous apparatus, which is similar to that induced by the puncture. Yet we must remember that it is possible to have septic fever without there being any glycogen in the liver, whereas the puncture of the brain produces no elevation of temperature under these circumstances. While we might assume, therefore, that the consumption of the glycogen in fever resulted from a stimulation of the nervous system, this hypothesis would not offer an explanation for the characteristic destruction of proteid material and for the fact that fever may occur in the absence of glycogen.

The hypothesis that the increased heat production in fever is merely an acceleration of normal metabolism—that it is due, in fact, to an " increased chemical tone"—meets with the serious objection that the metabolism in fever is not only quantitatively increased, but is qualitatively altered, especially as regards the consumption of proteids.

It seems to me very probable that the agent causing the fever actually destroys the cell proteids in various parts of the body. What becomes of the non-nitrogenous constituents of the injured proteid molecules is at present unknown to us.

[47] Krehl and Kratzsch, Arch. f. exp. Path., vol. xli. p. 185; Hirsch and Müller, Arch. f. klin. Med., vol. lxxv. p. 287; Zuntz, Ztrbl. f. d. med. Wiss., 1882, p. 32.

[48] Hirsch and Rolly, Arch. f. klin. Med., vol. lxxv. p. 307; Rolly, ibid., vol. lxxviii. p. 248.

Yet exact information on this point appears to be essential before we can explain the abnormal course of the metabolism in fever and the fact that the heat formed does not furnish a sufficient stimulus to the mechanism that controls heat loss.

The Heat-Regulatory Mechanism in Fever. — In the healthy individual a proper heat regulation cannot be maintained unless certain parts of the mid-brain are intact. If these be destroyed, or if the spinal cord be cut at a high level, the temperature depends largely upon that of the surroundings, just as is the case in cold-blooded animals.

It would seem probable that this nervous mechanism, which regulates the temperature of the body, is diseased in fever. The observations bearing on this question have dealt, for the most part, with the effect of procedures which withdraw heat from the body, and experiments on men as well as animals have shown that if heat be artificially withdrawn from the body by cold baths, etc., then the compensatory increase in the heat production is less if the animal has a fever than if it be normal. In certain experiments on animals, indeed, there may be absolutely no increased production of heat under these circumstances.[49]

It follows that the temperature of febrile animals is more readily reduced by artificial cooling than is that of normal animals, and that, other things being equal, the patient with fever may be cooled off with comparative ease. It is also probable that his temperature may be more easily raised by artificial means. For example, animals more readily acquire a high temperature from warm surroundings if they have been previously treated with injections of pus.[50] In apparent con-

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[49] Liebermeister, Path. d. Fiebers, p. 341; Colasanti, Pflüger's Arch., vol. xiv. p. 125; Finkler, ibid., vol. lix. p. 98; Zuntz, Du Bois' Arch., 1882, p. 43.

[50] Dobrzanski and Naunyn, Arch. f. exp. Path., vol. i. p. 181; Finkler, loc. cit.

tradiction to these facts is the observation that the temperature of an animal with fever is sometimes made higher by exposure to cold, possibly because the cold increases the heat production within the body. Narcotic drugs render it impossible to produce fever by certain artificial means,[51] probably because they effect the heat regulating centres.[52]

It is a matter of common clinical experience that the temperature of patients with fever is less resistant to external influences than is that of normal individuals. This lack of resistance differs in amount in different diseases and may even vary at different periods of the same disease. During typhoid fever, for example, the temperature can usually be reduced more readily in the later than in the earlier weeks of the illness. One reason why fever patients are particularly susceptible to the antipyretic action of the cold bath is, that their cutaneous vessels react abnormally to stimuli. It is when these vessels remain dilated for a considerable period after the cold bath that the most marked falls in temperature occur.[53] The antipyretic drugs also reduce the temperatures of fever patients much more effectually than they do those of normal individuals; and here again these drugs are not equally effective in all cases nor in the same case at all stages of the disease.[54] Thus we see that the temperature does not resist external influences during fever so well as it does during health, and that this is so, partly because the regulatory mechanism is less effective, and partly because the peripheral blood-vessels react abnormally to stimuli.

Even during the convalescence from infectious diseases, the temperature regulation is often imperfect. Patients, who are recovering from typhoid fever, for example, easily acquire

[51] Mendelson, Virch. Arch., vol. c. p. 274.
[52] Rumpf, Pfluger's Arch., vol. xxxiii. p. 538.
[53] Finkler, Kongr. f. in. Med., 1888, p. 314.
[54] Gottlieb, Arch. f. exp. Path., vol. xxvi. p. 419; vol. xxviii. p. 167.

an elevation of temperature after eating large amounts of food or after excessive exercise; apparently because they cannot eliminate the large quantity of heat that has been suddenly liberated in their bodies. An analogous condition is seen in many captive animals, and it seems as if their temperature regulation is injured to a certain extent by the life of captivity. Thus Finkler has observed a temperature of 40° C. (104° F.) in starving guinea-pigs after a full meal.

All these facts point to some changes in that part of the brain which regulates the body temperature. The question naturally arises, Will patients with fever eliminate normally the extra heat that is set free in the body when large quantities of proteid food are taken, or when the individual exercises? Unfortunately, we have but little satisfactory evidence on these points, for, in the first place, it is not easy to feed fever patients with large amounts of food,[55] and in the second, the observations that muscular exercise tends to elevate the temperature of tuberculosis patients [56] do not, to my mind, settle this question decisively. Nevertheless, some importance must be allowed to the clinical observations that large amounts of food and much exercise tend to elevate the temperature of weakly individuals, convalescents, and of those with slight fever; and it really seems as if these patients eliminate the extra heat produced less well than do normal individuals. Lang has found that after taking food there is an increased elimination of water from the bodies of both normal and feverish individuals, though it is slightly less in the latter.[67] Since he has also shown that the fever itself does not affect the elimination of water from the skin, it would appear as if the feverish patient is able to eliminate the extra heat that follows the

[55] For this reason the results of Bauer, Arch f. klin. Med., vol. xxiv. p. 60, and of v. Hosslin, Virch Arch, vol lxxxix p 95, are not decisive

[56] Ito, Diss. Erlangen, 1899.

[57] Lang, Arch f klin Med, vol lxxx p 353

taking of food fairly well, even though he does not eliminate the extra heat which causes the fever.

The elevated temperature of fever is produced mainly by the insufficient loss of heat from the body. Possibly, indeed, this is the primary factor that causes the rise in temperature, though it seems more probable to me that the excessive heat production is also of some importance. Various possibilities as to the causal relation between these two processes must be considered. In the first place, the cause of the fever may affect primarily the central nervous system, producing, on the one hand, an increased production of heat, and, on the other, an insufficient elimination. Liebermeister,[58] advanced such an hypothesis,—viz., that in fever the heat regulatory centre is " set at a higher level" than normal, and that it tends to maintain the temperature of the body at this new level in the same way that it usually tends to maintain the normal temperature. We now know, however, that the temperature in fever is not maintained at its new level with the same degree of resistance to external influences as it is in health.

According to a second hypothesis, the essential feature of fever is the insufficient heat elimination, the increased proteid destruction being non-essential and of the same character as that seen in various cachectic diseases.

To my mind, however, it seems most probable that the agent causing the fever destroys the proteids and glycogen of the body in some abnormal manner, and so increases the heat production. The products of this abnormal metabolism, however, do not cause a sufficient elimination of heat, either because they do not furnish the proper stimulus to the heat regulating mechanism, or because the irritability of this mechanism has been reduced in some peculiar manner.

[58] Path. d. Fiebers.

The Causes of Fever. (*a*) *Bacteria.*—Various causes may give rise to fever. In the first place, fever may be produced by the entrance of living or dead bacteria, or of their products, into the blood. Yet the mere presence of micro-organisms in the circulation does not necessarily raise the temperature of the body, and many bacteria which produce fever in certain animals will fail to do so in others. Indeed, an animal may die from an infection and its heat production may be markedly increased, and yet, on account of the elimination of the extra heat from the body, there may be no rise of temperature.[59] Protozoa may also give rise to fever, as in the case of malaria and of certain experimental infections.[60]

The substances that cause the fever are very possibly of a proteid nature, for complex substances isolated from the bodies of bacteria may give rise to fever if injected into men or animals.[61] It is questionable, however, whether these substances are themselves proteids, or whether it is merely difficult to separate them from proteids. Some have attempted to show that there is a non-proteid, fever-producing substance common to all bacteria,[62] but the evidence of this is very inconclusive.

(*b*) *Aseptic Fevers.*—Though bacteria and bacterial products are undoubtedly the most important causes of fever, they are not the only ones. Fever may be produced by the destruction of large numbers of cells in the body, even though micro-organisms play no part in the destructive processes. As examples of such, we may recall the fever that so frequently

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[59] Riethus, Arch. f. exp. Path., vol. xliv. p. 253.

[60] Pfeiffer, in Penzoldt-Stintzing's Handbuch; Krehl and Matthes, Arch. f. exp. Path., vol. xxxviii. p. 284.

[61] H. Buchner, Berl. klin. Wochens., 1890, No. 10, and Münch. med. Wochens., 1891, No. 49; Krehl, Arch. f. exp. Path., vol. xxxv. p. 222.

[62] Centanni, Deut. med. Wochens.; 1894, Nos. 7 and 8; Voges, Ztft. f. Hyg., vol. xvii. p. 474.

follows a simple fracture,[68] or that which may follow large interstitial hemorrhages. The fibrin ferment which is formed during the coagulation of blood may also cause an elevation of temperature.[64]

The fact that fever may be produced by bodies not derived from bacteria has led to careful studies concerning the action of numerous chemical substances upon the temperature of warm-blooded animals.[65] These studies have demonstrated that fever may be produced by the injection of various forms of proteids, whether the latter are assimilated or not, and whether they be of complex or comparatively simple structure. Elevations of temperature also follow the injection of many organic compounds and salts. Different animals, however, differ in their susceptibility to the action of these substances.

Is it not possible that a single chemical substance or class of substances is the cause of all fevers? Some have thought, for example, that the fibrin ferment might play such a rôle, but Hammerschlag[66] has shown that in many fevers this substance is not increased in the blood.

Albumoses, on the other hand, may be demonstrated in the urine of nearly all fever patients, whether the fever was of infectious or of other origin.[67] It is thus certain that proteid material undergoes hydrolytic cleavage during all forms of fever, even those caused by the introduction of simple chemicals into the body. The introduction of albumoses themselves into the body will give rise to fever, though it is possible that some contamination in the albumoses is the immediate cause

[63] Volkmann and Genzmer, Volkmann's klin. Vortr., No. 21.

[64] Edelberg, Arch. f. exp. Path., vol. xii. p. 283.

[65] Krehl, Arch. f. exp. Path., vol. xxxv. p. 222; Krehl and Matthes, Arch. f. klin. Med., vol. liv. p. 39; Klemperer, Naturforcherversammlung, 1903, vol. ii. p. 67.

[66] Arch. f. exp. Path., vol. xxvii. p. 414.

[67] Krehl and Matthes, Arch. f. klin. Med., vol. liv. p. 501; Schultess, Arch. f. klin. Med., vol. lviii. p. 325; vol. lx. p. 55.

of the elevation of temperature.[68] On the other hand, albumoses may appear in the urine without there being any fever,[69] so that if we assume that albumoses do cause fever normally, it is necessary to assume also that this effect can only result from certain forms of these proteids, and that other forms, not distinguishable chemically, produce no such effect.

At any rate, the proteid decomposition in fever pursues a peculiar course, and the hypothesis that the products of this abnormal decomposition directly cause the fever is an exceedingly attractive one. According to such an hypothesis, the substances that produce the fever do so by primarily causing this abnormal proteid decomposition. The resulting products then give rise to the fever in the manner that has been already indicated.

(c) *Nervous Fevers.*—It is probable, therefore, that the majority of all natural fevers are due to intoxications or infections. Some fevers are possibly of a different character, however, for it seems probable that the nervous centre which regulates the temperature of the body may be primarily diseased, and that it may be influenced by impulses from other parts of the central nervous system. Many observations, purporting to be examples of such a nervous fever, will not stand the scrutiny of a rigid criticism. For example, in poliomyelitis, poliencephalitis, and meningitis the elevation of temperature is probably due to the infection; while in other conditions, such as large cerebral hemorrhages, it may possibly be caused by the absorption of the fibrin ferment or of the products resulting from the destruction of large numbers of cells.

In other conditions, the nervous lesion seems to exert a more direct influence upon the bodily temperature. At times, general convulsions, associated with stupor, lead to excessive elevations of temperature, and at other times, when the con-

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[68] Krehl and Matthes, Arch. f exp. Path., vol xxxvi. p. 437.

[69] See Schultess, Arch. f. klin Med, vol lx. p 55.

vulsions are produced by certain drugs, there may be an actual reduction of temperature.[70] In the latter instances the heat regulation is affected, and it seems as if the poisons leading to the convulsions likewise diminished the production of heat in the body.

. We know that muscular movements will raise the temperature of even a healthy person, if the elimination of heat is interfered with, which fact has also been proved experimentally on animals.[71] If, however, the extra heat that is liberated during exercise can be eliminated, no rise of temperature results. As a rule, therefore, convulsions do not materially alter the body temperature. A rise of temperature is especially apt to be produced by convulsions when there is reason to believe that the heat-regulating mechanism is paralyzed.[72] For example, fever is rarely present in the earlier stages of tetanus, and the rise of temperature toward the end of the disease would appear to be caused by a paralysis of the heat-regulating centre. The high temperature that has been observed in many cases of status epilepticus is probably to be explained in a similar manner. Possibly, also, the elevations of temperature in hysterical individuals, which have been described by some writers, are of this character,[73] though, never having witnessed a true hysterical fever, I personally feel somewhat sceptical as to its existence.

In another group of cases, fever is associated with gross lesions of the central nervous system, and neither infection, resorption of the products of tissue disintegration, nor convulsions can be held responsible for its presence. Brain tumors

[70] See Harnack and Schwegmann, Arch. f. exp. Path., vol. xl. p. 151; Harnack, ibid., vol. xlv. pp. 45, 447.

[71] Leyden, Virch. Arch., vol. xxvi. p. 538; Kionka, Internat. Arch. f. Phar., vol. v. p. 111.

[72] Wunderlich, Arch. f. Heilkunde, 1864, p. 205; Erb, Arch. f. klin. Med., vol. i. p. 175.

[73] Dippe, Arch. f. klin. Med., vol. lxiv. p. 212.

and other pathological conditions may thus produce a fever, and it seems very probable that the elevation of temperature is then due to the direct action of these pathological processes upon the mechanism regulating the heat of the body.

Experimentally, it is possible to produce fever in animals by injuring the brain. Injuries to various parts of the cerebrum will sometimes cause an elevation of temperature, but this elevation can be caused in almost every case if a long needle be thrust into the mid-brain of rabbits.[74] The fever produced by such a puncture begins several hours after the operation and continues for days. It may reach a considerable height. The production of heat in the body is increased, and the loss of heat is also increased, but to a lesser degree. The loss of heat by evaporation from the skin is relatively greater than it is in the case of infectious fevers. Furthermore, the increased heat production is almost entirely due to the increased consumption of non-nitrogenous material, which fact also serves to differentiate this from ordinary fever, in which a characteristic hydrolytic cleavage of proteids takes place.[75] During the fever resulting from a puncture of the brain the liver is the warmest organ of the body,[76] and the glycogen stored up there rapidly disappears. Indeed, unless there is a store of glycogen in the body, no rise in temperature follows the puncture of the brain.[77] It is therefore apparent that the elevation of temperature caused by puncture of the brain differs from that due to an infection in several important particulars.

It is very questionable whether fever is ever caused by

[74] Aronsohn and Sachs, Pflüger's Arch., vol. xxxvii p 232; Gottlieb, Arch. f. exp. Path., vol. xx. p. 167; Schultze, Arch. f. exp. Path., vol. xliii. p. 193; Aronsohn, Virch. Arch., vol. clxix. p. 501.

[75] Rolly, Arch. f klin. Med., vol. lxxviii. p. 289; Martin, Arch. f. exp. Path., vol. xl. p. 453.

[76] Hirsch and Rolly, Arch. f. klin. Med., vol. lxxv. p. 307.

[77] Rolly, loc. cit.

reflexes. The elevations of temperature which may occur during biliary colic and those which may follow urethral operations (catheter fever) are often regarded as instances of reflex fevers. Yet, in my opinion, it is much more probable that we are here dealing with fevers caused either by the absorption of toxic products or by actual infections. Possibly an investigation into the metabolism in such cases might give some indication as to the true nature of the fever.

Elevations of temperature have been observed after injuries to the spinal cord. Such elevations occur most frequently in association with severe contusions of the cervical region, produced by fractures of the corresponding vertebræ. Temperatures as high as 42° to 44° C. (106.5° to 111° F.) have been observed in such conditions.[78] It is possible to produce the same effect experimentally by crushing the uppermost part of the cervical cord of large dogs.[79] After such injuries the temperature does not always become elevated, and it may, indeed, fall. These varying results of the experiment are due to the fact that, if the cord of a warm-blooded animal be severed high up, the body temperature becomes a plaything of circumstances. When the temperature of its surroundings is high, the heat production is increased, and when the surrounding temperature is low, the heat production is diminished; in other words, there is no regulation of the production of heat in the body.[80] This is one reason why animals easily become overheated or cooled off after they have sustained severe contusions of the cervical cord.

Other factors besides the surrounding temperature also play a part in the elevation of the temperature that takes place in cord injuries, though upon these points we are less certain. It is possible, for example, that the peripheral circulation is so

[78] v. Recklinghausen, Allg. Path., p. 463.

[79] Naunyn and Quincke, Arch. f. Anat. u. physiol., 1869, pp. 174, 521.

[80] Pflüger, Pflüger's Arch., vol. xii. p. 282.

altered that the loss of heat from the body is diminished. Furthermore, the crushing of the cord, which manner of injury seems to be an important requisite for a high temperature, may possibly produce an irritation of the corresponding muscles, and so directly increase the production of heat in the body. This is apparently the reason why the elevation of temperature is more likely to take place in men and large dogs than it is in small animals. The former have a relatively small surface from which to lose heat and a relatively large musculature in which an increased heat production can take place. We see therefore that the rise of temperature that may follow cord injuries is due, partly, to a loss of heat regulation, and partly, in all probability, to an increased production and a diminished loss of heat from the body. The condition, therefore, differs essentially from that present in true fever.

The Causes of Variations in the Clinical Picture of Fever. —These depend, in the first place, upon the cause of the fever. Most fevers are of bacterial origin, and, as is well known, bacteria may vary in their virulence, conditions of growth, and duration of life. So far as malarial fever is concerned, we know that the paroxysms occur when the causative organisms are at a particular stage of development.

In the second place, the clinical picture presented by fever depends largely upon the condition of the individual affected; upon his strength, nutrition, and degree of immunity. During epidemics, different symptoms occur in different individuals. We may say, in general, that young and strong patients react with a higher fever to an infection than do old and weakly ones. Indeed, the temperature may actually fall in the latter class of patients. We possess analogous experimental observations, for it is impossible to produce fever by the injection of certain chemicals into fasting animals, whereas the same chemicals will regularly cause a fever in well-fed animals.[81]

[81] Krehl and Matthes, Arch. f. exp. Path., vol. xl p. 430.

Bacterial infections, on the other hand, may cause an elevation of temperature whether the animal be starving or well fed.

The numerous other symptoms seen in fever are also subject to considerable variations. These depend in part upon the height of the temperature, for this influences the rate of the proteid and other decompositions, as well as the cardiac and respiratory rates. Yet no exact ratio exists between the severity of these symptoms and the degree of temperature, because other factors, especially toxic influences, play so great a rôle. This has already been discussed so far as the pulse-rate is concerned (see page 79).

Indeed, we may say, in general, that the symptoms of intoxication predominate in the clinical picture of fever, and that many of the phenomena which were formally attributed to the high temperatures are now ascribed to the action of toxins. Thus the psychic changes, the gastro-intestinal disturbances, and the susceptibility of the respiratory tract to complicating inflammations, all these are of toxic rather than of thermic origin. They are rarely seen in the " aseptic fever" following simple fractures, and they are most prominent in such pronounced intoxications as typhoid fever. These symptoms also depend to a certain extent upon individual peculiarities, and heavy drinkers, for example, are very prone to show serious nervous manifestations.

The Nutrition in Fever.—The nutrition is always impaired in fevers of long duration, partly because of the increased proteid consumption, partly because the patients do not take a sufficient quantity of food. Their appetites are often very poor, though this may not be the case in the hectic fever of tuberculosis. For these reasons most patients with fever become emaciated and weak, and the weakness is often greater than can be accounted for by the lack of food alone; being dependent, as we have seen, upon the excessive consumption of the proteid material of the body.

On the other hand, in long-continued infections, a tendency to limit the metabolic processes is often manifest, and in the terminal stages of chronic diseases the proteid decomposition and the total oxidations in the body often reach a surprisingly low level. This adaptation enables many a person to undergo a long-continued illness which would otherwise prove fatal. Though the excessive consumption of proteid material is common to all forms of fever, it seems very probable that certain infections are particularly harmful in this respect.

The cause of the various forms of cellular degeneration that occur so frequently in fever is not yet definitely determined. Some believe that the high temperature may cause the degenerative changes,[82] whereas others hold that the temperature alone will not produce them.[83] It is impossible at present to reconcile these varying views.

The Water Retention in Fever.—Years ago, Leyden [84] made the observation that patients with fever frequently lose but little weight during the course of the acute process,—*i.e.*, at the time when the consumption of material in the body is most active, but that the principal loss in their weight takes place during convalescence. He explained these results by assuming that there is a retention of water in the body during fever. From that time up to the present this question has awakened general interest.

Yet we need more accurate data concerning this retention of water in fever, for not all investigated cases have yielded identical results.[85] Indeed, a complete and accurate determination of the water losses in fever has never been made. As a rule, the urine is diminished in quantity, and the absolute loss

[82] Liebermeister, Path. d. Fiebers, p. 427; Litten, Virch. Arch., vol lxx. p 10; Ziegler, Kongr. f. in. Med., 1895, p. 345; Werhowsky, Ziegler's Beitr., vol. xviii. p. 72.

[83] Naunyn, Arch. f. exp. Path., vol. xviii. p. 49.

[84] Arch. f. klin. Med., vol. v. p. 366.

[85] See Kohlschütter, Volkmann's Beitr., No. 303.

through the skin is equal to or less than that in health; but the loss through the lungs is increased.[86] From these isolated observations it is impossible to tell accurately whether the total loss of water from the body is increased or diminished during fever. The low quantity of chlorides in the urine during certain fevers has been explained on the assumption that a salty liquid is retained in the body; but, in our opinion, this assumption is hardly justified.

Despite our lack of direct observations on these points, it seems highly probable that a retention of water does take place in the bodies of many fever patients. The exact conditions upon which this retention depends are, however, at present unknown to us, though we know that various cachectic conditions, such as carcinomatosis, may lead to a retention of water in the body. In another place we have expressed the view that an insufficient evaporation from the skin was one of the main causes of the heightened temperature of fever.

The Significance of Fever.—Whether or not the elevation of temperature is of advantage to the infected organism is a subject that has engaged the attention of physicians from the most remote times down to the present. Three conflicting views have been advocated. According to the first, the elevation of temperature is in itself dangerous to the patient,[87] and may even be the cause of death; according to the second, the danger of the infectious process depends only to a very slight extent upon the high temperature; and according to the third, the high temperature is advantageous, for by this means the infected body is "cleansed by fire." [88] The treatment of fever must depend to a large extent upon the view that is accepted, consciously or unconsciously, by the physician.

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[86] Lang, Arch. f. klin. Med., vol. lxxix. p. 343.

[87] Liebermeister, Path. d. Fiebers, p. 423.

[88] Pflüger, Pflüger's Arch., vol. xiv. p. 502; see Unterricht, Volkmann's Vortr., N. F., No. 159.

Is the elevation of temperature in the course of an infection useful, harmful, or of no particular significance? So long as the elevation remains within moderate limits, it may certainly be regarded as relatively harmless. The rapid pulse and respirations, the loss of appetite, and the possible parenchymatous degenerations of the organs, in so far as they are directly caused by the temperature, are not in themselves very dangerous. If, on the other hand, the elevation of temperature is very great, it may certainly be harmful and the same dangers are threatened as in a heat stroke. Yet such dangerously high temperatures are comparatively rare in fever, and the reason why a high temperature is generally regarded as a bad sign in an infectious disease is that it indicates a severe infection. This is well illustrated by the fact that high temperatures in malaria are generally regarded with a certain amount of indifference, whereas the same temperatures in typhoid fever or pneumonia would be looked upon with alarm.

Whether the elevation of temperature is directly beneficial to the infected organism or not, is a question that is not so easily settled. In recent years there has been a tendency to apply the Darwinian theory to pathological processes in general, and to say, for example, that fever could never have survived throughout immeasurable time were it not inherited as a useful weapon in the struggle for existence. Yet one may question to what extent the Darwinian theory applies to pathological conditions,[89] and it seems equally reasonable to regard fever as a blind reaction against an injury, possibly useful or possibly harmful. The question is not one that can be solved by such philosophical considerations, and the final answer must be based upon established facts, derived either from bedside observations or from animal experiments.

Unfortunately, clinical studies have done little to solve this problem. We have, it is true, accumulated extensive statistics

See Ziegler, Münch. med. Wochens., 1896, No. 43.

on the course of infectious diseases, especially of typhoid fever, under the expectant and the antipyretic forms of treatment. Yet, even though we acknowledge the advantage of the latter treatment, we are helped but little to a solution of our problem, for cold water not only lowers the temperature of the body, but it influences the disease in many other ways, and antipyretic drugs introduce abnormal chemical processes into the metabolism.

It is possible that at a higher temperature the growth or virulence of the micro-organisms which cause the disease may be diminished. At present, however, we are unable to say definitely to what extent this actually occurs in disease.

We do possess, however, a number of observations on the effect of increasing an animal's temperature after it has been artificially infected. Infections with diphtheria bacilli, chicken cholera bacilli, and pneumobacilli run a milder course in rabbits if the temperature be artificially elevated by puncture of the brain,[90] and intoxications with hydrolytic ferments likewise are less virulent at higher temperatures.[91] The same has been found to be true for erysipelas infections in rabbits,[92] and the number of such examples could be still further multiplied.

Perhaps the action or formation of antibodies is favored by the high temperature. At any rate, Kast found that Pfeiffer's antibody against typhoid bacilli worked better at high temperatures,[93] though, on the other hand, antipyretic treatment does not seem to influence the formation of the immune body in man.[94]

We possess, therefore, some noteworthy experiments which support the view that the elevation of temperature dur-

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[90] Loewy and Richter, Virch. Arch., vol. cxlv. p. 49.

[91] Hilderbrandt, Virch. Arch., vol. cxxi. p. 1.

[92] Filehne, Jour. of Physiol., vol. xvii.

[93] Kast, Kongr. f. in. Med., 1896, p. 37; Paech, Diss. Breslau, 1900.

[94] Lemaire, Arch. internat. de pharacodyn., vol. v. p. 225; Schütze, Ztft. f. Hyg., vol. xxxviii. p. 205.

ing an infection is directly beneficial to the infected organism. It must be admitted, however, that only a beginning has been made, and that more observations are necessary before the question can be regarded as definitely settled, and before we shall know whether it is the increased temperature itself or some associated changes in metabolism that benefits the patient.

The Temperature in Collapse.—We have had frequent occasion to mention that the temperature during fever is subject to great variations, and that it tends to rise or fall from relatively insignificant causes. A great fall of temperature during an infection has long been recognized as a dangerous symptom, mainly because it so frequently heralds the onset of collapse. Such a fall is especially apt to occur in weak individuals. This has been observed experimentally. The ordinary fever-producing agents may cause a reduction in an animal's temperature if they are given in large amounts, or if the animals used are very " weak" or " non-resistant." It is difficult to say what constitutes this " weakness" or " lack of resistance" on the part of infected individuals, though it is very possible that the condition of the circulation plays an important rôle.

Not only the resistance of the individual, but the kind and quantity of toxins are of importance in the production of collapse. The same substance that will give rise to fever in small doses will lead to collapse if given in large doses. This is well illustrated in the case of Koch's tuberculin.[95] If this substance be given to animals in very large doses, the production of heat in the body is actually diminished, and in the fatal cases only fifty-three per cent. of the normal amount of heat may be produced. At autopsy the vessels in the abdomen, and especially those belonging to the intestines, are found to be dilated. This finding agrees with the observations of Romberg, Pässler, and Bruhns (see page 113), who showed that

[95] Matthes, Arch. f. exp. Path., vol. xxxvi. p. 437; vol. xxxviii. p. 299; Krehl, ibid., vol. xxxv. p. 222.

the circulatory failure in infectious diseases is principally caused by a central vascular paralysis, affecting especially the splanchnic vessels. The dilatation of these vessels allows so much blood to collect in them that the heart is no longer properly filled from the veins, the general blood-pressure falls, and the activity of the muscles becomes so reduced that, in spite of the fact that the heat losses are greatly diminished, the body is no longer able to maintain its normal temperature. Thus we see that the fall of temperature in collapse occurs at a time when less heat than normal is produced in the body.

A certain antagonism exists, therefore, between fever and collapse. In fever, both the heat production and the heat losses are increased, the former being especially accelerated. In collapse, both of these are diminished, but the heat production is more diminshed than is the heat loss. \ On the other hand, fever and collapse resemble each other in certain respects, for in both too small an amount of blood passes through the cutaneous vessels.[96] Indeed, they tend to shade into each other, and, as we have seen, the one or the other may result from the same cause, depending upon the factors already described.

Subnormal Temperature.—Subnormal temperatures are seen not only during collapse from infectious diseases, but also after extensive injuries, severe hemorrhages, long-continued narcosis, perforative peritonitis, and various other severe lesions within the peritoneal cavity. It is possible that in many of these the same conditions are present as in collapse; yet it is quite wrong to regard all subnormal temperatures as symptoms of collapse.[97]

Subnormal temperatures are more common than is generally supposed. They are often seen during convalescence from infectious diseases, and in such instances they are generally due to a diminished production of heat combined with an in-

[96] Maragliano, Ztft. f. klin. Med., vol. xiv. p. 309; vol. xvii. p. 291.
[97] Jannsen, Arch. f. klin. Med., vol. liii. p. 247.

efficient heat regulation. A subnormal temperature frequently accompanies intoxication with alcohol or related drugs. These lessen the rate of oxidation in the body,—*i.e.*, they diminish heat production and, in addition, they interfere with the mechanism regulating the loss of heat from the skin.[98] Consequently, an intoxicated man is less able to withstand cold than is a healthy individual, and if exposed to cold, the temperature of his body is more liable to fall.

When the temperature of the body becomes very low, narcosis and finally a general paralysis results. The narcosis will, in turn, favor a further lowering of the temperature, for the body can no longer increase its production of heat by muscular activity. Even in ordinary sleep the heat regulation is less efficient than during the waking hours, and this lack of regulation is much more marked during deep narcosis. For these reasons, the danger of freezing to death is best combated by continued muscular movements, for these not only increase the production of heat, but they reduce the tendency to go to sleep.

We do not know how low the temperature may fall without causing death,. though it is certain that both men and animals have recovered from very low temperatures.[99]

[98] Rumpf, Pflüger's Arch., vol. xxxiii. p. 538.
[99] Jannsen, loc. cit., and Cohnheim, All. Path., vol. ii. p. 489.

CHAPTER XI.

THE SECRETION OF URINE.

THE major portion of the solid waste products that arise in the body leave it by way of the kidneys. We have already had occasion to describe many of these substances, and it is not our purpose to review in this place the origin of each one of them, but rather to deal with the mechanism of secretion itself; though it must be admitted that it is often impossible to draw a sharp line between this secreting mechanism and the products that are eliminated.

The composition of the urine depends partly upon the condition of the secreting cells in the kidneys and partly upon the quality and quantity of blood which passes through these organs. These factors are more or less interdependent upon one another. For example, if the blood-stream through the kidneys be slowed, not only does less blood come in contact with the secreting cells but these cells are liable to suffer in structure and function. On the other hand, if the renal cells are primarily injured, this frequently affects the circulation through the kidneys. It is often very difficult, therefore, to tell which part of the renal apparatus is primarily affected.

The Effect of an Increased Flow of Blood through the Kidneys.[1]—It is a general rule that the quantity of urine secreted varies directly with the quantity of blood that flows through the kidneys. It likewise varies with the difference between the pressure of the blood in capillaries and the pressure of the urine within the uriniferous tubules. (Finally it varies directly with the pulse pressure (the difference between the maximum and minimum blood pressures).[2]—ED.)

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[1] See Munk and Senator, Virch Arch., vol. cxiv. p. 1; Spiro and Vogt, in Asher-Spiro Ergebnisse, vol. i. p. 414.

[2] Erlanger and Hooker, Am. Jour. of Physiol., vol. x.

When the total quantity of urine is increased, the percentage of solid materials present decreases, and *vice versa;* yet this percentage of solids nearly always remains within certain limits, rarely going above twelve per cent. or below three-tenths per cent. The relation between the total quantity of solids excreted and the total quantity of urine seems to be subject to considerable variation, and the different solids often vary independently of one another. The total quantity of urea, for example, varies directly with the quantity of blood that flows through the kidneys, whereas the total quantity of sodium chloride is almost independent of this blood-flow.

Whenever more blood flows through the kidneys, therefore, the amount of urine is increased. The cause of the increased blood-flow may lie either in a higher arterial pressure, unaccompanied by a corresponding contraction of the renal vessels, or it may be due to a local dilatation of these vessels, while the general blood-pressure remains constant.

Many forms of chronic nephritis are accompanied by a high blood-pressure (see page 50), and this always causes an increased secretion of urine, if a sufficient number of functioning renal cells are present and if the increase in the general blood-pressure is not accompanied by a constriction of the renal vessels of such a degree that it would prevent a more rapid blood-flow through the kidneys. As we have said, the increased elimination of water in such cases reduces the percentage of solids in the urine. The absolute excretion of the different solids, however, in these forms of nephritis varies greatly,[3] being dependent, apparently, to a great extent upon the condition of the epithelial cells.

The increased blood-pressure that follows the administration of digitalis to patients with heart disease also frequently causes an increased elimination of urine, because the renal

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[3] Fleischer, Arch. f. klin. Med., vol. xxix. p. 129; v. Noorden, Path. d. Stoffwechsels, p. 364.

circulation is improved. Whether or not other conditions associated with high arterial pressure, such as certain forms of arteriosclerosis and of "idiopathic" heart hypertrophy, likewise increase the urine, is still uncertain.

Diabetes Insipidus.—The second condition leading to an increased flow of blood through the kidneys is a local dilatation of their vessels, the arterial pressure remaining constant; as can be experimentally proven by cutting the renal nerves.

Such a dilatation of the renal vessels is a possible cause of diabetes insipidus, a disease which is characterized clinically by the excretion of large amounts of dilute, sugar-free urine, without there being any associated increase in the general arterial pressure. The excessive amount of urine frequently carries out with it demonstrable quantities of inosite, and at times the total quantity of urea is also increased. This latter increase is caused by the large amounts of food eaten, for many of these patients, for some unknown reason, have excessive appetites, just as have patients with diabetes mellitus.

We really know very little concerning the etiology of diabetes insipidus. It certainly occurs sometimes as a family disease.[4] In some cases the blood is more dilute than normal, and this may be instrumental in causing the polyuria; yet this finding is by no means a constant one. At other times anatomical lesions of the cerebellum, the pons, or the medulla have been found at autopsy,[5] findings which well accord with the experimental observation that injuries to corresponding parts of the brain in animals may lead to polyuria.[6] Yet there is some uncertainty as to the exact part of the brain that must be affected in order to produce this increased flow of urine.

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[4] Weil, Virch. Arch., vol. xcv. p. 70.

[5] Ebstein, Arch. f. klin. Med., vol. xi. p. 344; Hoffmann, Lehrbuch d. Konstitutionskr., p. 342.

[6] Claude Bernard, Leçons de Phys.; Eckhard, Beitr. z. Anat. u. Phys., 4, 5, and 6.

The evidence at our disposal, therefore, seems to favor the hypothesis that diabetes insipidus is due to some abnormal vasomotor influences, which cause a local dilatation of the renal arteries. It must be acknowledged, however, that this hypothesis does not explain very satisfactorily all of the symptoms of diabetes insipidus, nor does it explain the relationship which seems to exist between this disease and true diabetes mellitus.

The Effect of a Diminished Flow of Blood through the Kidneys.—If the quantity of blood that flows through the kidneys be diminished, a small amount of highly concentrated urine is secreted, and the total excretion of urea is diminished.

The cause of such a diminished blood-flow may be either local or general. Locally a contraction of the renal vessels will diminish the renal circulation, and it may do so even though the general blood-pressure be increased from a contraction of many other arteries. This local constriction of the renal arteries is the cause of the diminished secretion of urine in asphyxia, in strychnine poisoning, and in epileptic and eclamptic convulsions.

In the second place, a diminished renal circulation may occur in the absence of any local constriction of the renal vessels, either because the general arterial pressure is reduced or because the pressure in the renal veins is raised. The reduction of the general arterial pressure may result from a wide-spread vasomotor paralysis or from a weakening of the left ventricle. The pressure in the renal veins may be raised, either by an occlusion of these veins or of the vena cava inferior, by an increase in the general venous pressure from a weakening of the right ventricle, or by a diminution in the aspirating action of the thorax. The most marked effect upon the renal circulation will naturally be produced when a lowering of the general arterial pressure is combined with a rise in the venous pressure. This combination occurs when both ventricles of the

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heart are weakened, and this is, indeed, the most frequent cause of an insufficient flow of blood through the kidneys. It is met with in many varieties of cardiac disease, whether these affect the endocardium, the myocardium, or the pericardium.

In many of these circulatory disturbances, proteids from the blood pass through into the urine; yet, since this is probably due to changes in the epithelial cells, we shall defer its consideration to another place.

The Effect of an Obstruction to the Escape of Urine.—The obstruction to the escape of urine may be situated within the kidney itself. The uriniferous tubules may be compressed by scar tissue, or their lumina may be occluded by casts or by precipitates of hæmoglobin, bilirubin, uric acid, calcium salts, etc. It is questionable, however, if any of the precipitates, with the exception of hæmoglobin, really oppose much resistance to the escape of urine and it is quite possible that they lie in the tubules merely because the amount of water secreted is insufficient to carry them away.

On the other hand, the obstruction to the exit of urine may be situated outside of the kidneys, in the lower urinary passages, and it may then be caused by calculi, tumors, scar tissue, etc. The effect which such obstructions exert upon the total quantity of urine secreted depends, in the first place, upon whether they obstruct the outflow from one or from both kidneys. If the former be the case, the affected kidney will eliminate less urine than normal, but the urinary material retained in the blood, will stimulate the other kidney and cause it to do extra work and to hypertrophy. The urine, as a whole, will not be greatly altered.

The effect of an obstruction upon the secretory activity of the affected kidney depends largely upon the degree of obstruction. If this be so complete that the urine is retained under a pressure amounting to sixty millimetres of mercury or more, the affected kidney ceases to secrete. If the obstruction

be less complete, so that the urinary pressure above the obstruction be less than sixty millimetres of mercury, then the secretion continues, but the rapidity of secretion diminishes in proportion as the pressure of retained urine increases.[7]   The details concerning the cessation of secretion are not very well understood.   At first, the retained urine merely serves to distend the urinary passages.   As the pressure increases, however, a portion of the urine appears to be resorbed through the cells of urinary tubules, which then become œdematous   Finally, the overfilled tubules and the swollen cells press upon the veins and capillaries and thereby diminish their size, and the rapidity of the flow of blood through the kidneys is lessened.   This, in turn, diminishes the secretion of urine.

If the obstruction to the flow of urine from a kidney be complete and permanent, then the corresponding kidney atrophies, and only a moderate grade of hydronephrosis develops. If, however, the obstruction be incomplete, or if it be more or less intermittent, then the structure and the function of the kidney are but little affected.   Its pelvis, however, gradually dilates, and an enormous hydronephrosis may be produced.

The Effect of Lesions of the Secreting Membrane.—We have already mentioned the susceptibility of the renal epithelium to changes in the quantity and quality of blood that passes through the kidneys.   Several membranes separate the blood in the capillaries from the lumina of the uriniferous tubules,— viz., the capillary walls, the basement membranes, and the epithelial cells.   The possibility exists, therefore, that lesions of any one of these might render the secretory apparatus abnormally permeable.   Apparently, however, lesions of the capillary walls are of comparatively little importance, and it may be said in general that the secretion depends rather upon the parenchyma cells than upon the endothelial lining of the capillaries. Indeed, wide-spread amyloid degeneration of the renal capil-

[7] Hermann, Wiener Sitzungsber., vol. xlvii. p. 317.

laries has been observed without any changes in the urine being present.[8]

All lesions of the epithelial cells, degenerative as well as inflammatory, and especially those lesions which involve the glomeruli, tend to diminish the secretion of water. Yet, in many cases of nephritis this tendency is more than neutralized by an associated increase in the amount of blood that flows through the kidneys, for, as we have seen, this tends to increase the excretion of urine. The quantity of urine, therefore, that is eliminated in pathological renal conditions depends mainly upon these two sets of factors: first, the degree and the extent of the damage to the secreting cells; and secondly, the quantity and quality of blood which comes in contact with them. In wide-spread acute nephritis, the excretion of water is nearly always diminished, whereas in chronic diseases of the kidney, especially if these be of limited extent, the effects of the increased work of the heart, the high blood-pressure, and the good renal circulation predominates, and such patients frequently secrete even more urine than does a normal individual. When, however, cardiac failure appears, and the general blood-pressure falls, then the amount of urine secreted by these patients is immediately diminished.

The excretion of solids follows about the same course as does that of the water, but less is known about them. Nitrogenous substances tend to increase with an increase in the quantity of urine; yet no very strict parallelism exists between the two. Other substances, especially the chlorides, seem to be excreted in quantities that are, to a great measure, independent of the total quantity of urine.[9]

Albuminuria.[10]—Although it has been generally consid-

[8] Litten, Berl. klin. Wochens., 1878, Nos. 22 and 23.

[9] Fleischer, Arch. f. klin. Med., vol. xxix. p. 129; v. Noorden, Deut. med. Wochens., 1892, No. 35, and in his Path. d. Stoffwechsels, p. 364.

[10] See Senator, in the Nothnagel System; Lüthje, Ther. d. Gegenwart, November, 1903.

ered that normal urine contains no albumin, recent work has
rendered it very probable that traces of albumin, as well as of
sugar, are normally present in this secretion.[11]   In order to
demonstrate this trace of albumin, however, it is necessary to
make use of special methods, such as the concentration of the
large quantities of urine.   This albumin is believed by Senator
and Mörner to be derived from the blood by a process of filtra-
tion through the glomeruli.   Owing to the presence of chon-
droidin-sulphuric or nucleinic acids in the urine, this albumin
may be precipitated by adding acetic acid.   One should there-
fore be cautious and not conclude too hastily that the precipi-
tate that so often results from the addition of acetic acid to
urine is necessarily due to mucin or nucleo-albumin, derived
from the cells of the kidneys or urinary passages.   The urine
may, however, contain true mucin, which is free of phospho-
rus and which is derived from the epithelium of the urinary
passages.[12]

There are persons who continually or at intervals show
easily demonstrable quantities of albumin in their urine with-
out feeling ill in any way.   We cannot assume that the kidneys
of such individuals are absolutely normal, in spite of the fact
that the ordinary symptoms of chronic nephritis are absent and
that the affected persons remain, to all appearances, perfectly
healthy.   It is certain that chronic nephritis frequently follows
quite a different course from that ordinarily described in our
text-books on medicine, and it is quite possible that many of
these cases represent exceedingly mild forms of the disease.

The So-Called Physiological Albuminurias.[13]—Aside from

[11] Posner, Virch. Arch., vol civ p. 497; Leube, Ztft. f. klin. Med.,
vol. xiii. p. 1; Mörner, Skan. Arch. f. Physiol., vol. vi. p. 332.

[12] Mörner, loc. cit.; v. Noorden, Arch. f. klin. Med., vol. xxxviii.
p. 204.

[13] Leube, Virch. Arch., vol. lxxii. p. 145, and Ztft. f. klin. Med., vol.
xiii. p. 1; Ther. d. Gegenw., October, 1902; Zeehuisen, Ztrbl. f. in. Med.,
1896, No. 2.

the class of cases mentioned in the last paragraph, there is a class of so-called physiological albuminurias, in which albumin in various quantities is present in the urine transitorily, without producing any symptoms. Here again it is often extremely difficult to decide whether such conditions are normal or whether they may not represent the milder stages of some really serious renal disease.

Among the causes which may lead to the excretion of albuminous urine are violent physical exertion [14] and cold baths.[15] It is interesting that the former leads to albuminuria more readily in the morning than in the afternoon, and more readily if the patient be standing than if he be lying, being similar in these respects to the so-called albuminuria of adolescence. It is possible that excitement causes albumin to appear in the urine in some cases.

In some instances, the taking of food has caused an albuminuria to disappear.[16] On the other hand, albumin may be excreted in the urine after the ingestion of food, and especially of many raw eggs.[17] It is possible that in these cases the eggs cause some intestinal disturbance, that the albumin is directly absorbed without being normally digested, and that this abnormal proteid in the blood is then immediately excreted by the kidneys.[18]

The Albuminuria of Adolesence.[19]—This form of albuminuria cannot be strictly separated from the preceding. It tends to occur during childhood and during the period of puberty, especially in weak and anæmic individuals. As a rule, the albumin appears in the morning, and exercise, excitement, or diatetic errors may all favor its appearance.

[14] Darling, Boston Med. and Surg. Jour., 1899, p. 231.
[15] Rem-Picci, cit. in Jahresber. f. Thierch., 1901, p. 820.
[16] Edel, Münch. med. Wochens., 1901, Nos. 46 and 47.
[17] See Neumeister, Physiol. Chem., p. 301.
[18] Ascoli, Münch. med. Wochens., 1902, No. 10.
[19] Lommel, Arch. f. klin. Med., vol. lxxviii. p. 541.

In many of these patients the amount of albumin in the urine follows a definite diurnal curve. During the night and immediately after rising, the urine contains no albumin, but during the morning hours the amount rapidly increases, reaching a maximum in the middle of the forenoon, and then finally it gradually diminishes or disappears in the afternoon. This diurnal variation may, however, be different in different cases.[20] It must be remembered, furthermore, that during definite renal disease, as at the termination of an acute nephritis, as well as in many forms of chronic nephritis, a very similar diurnal variation in the excretion of albumin is present.

The most important factor that influences the albuminuria in these cases is the change from the recumbent to the erect posture. Exertion, excitement, dietetic and alcoholic excesses also frequently seem to exert an influence, but the degree to which they do this seems to vary in individual cases. Many facts would seem to indicate that circulatory changes cause this form of albuminuria, though what the nature of these changes is still remains very uncertain. (When a normal individual changes from the recumbent to the erect posture, it has been shown that, although the maximum blood-pressure is increased, the difference between the maximum and the minimum pressures, the so-called pulse-pressure (see page 109) is diminished. This diminution in the pulse-pressure is accompanied by a lessened secretion of urine in normal individuals and in one patient, at least, who had a physiological albuminuria, it was regularly accompanied by an increased elimination of albumin. This increase also occurred when the pulse-pressure was lessened by some other causes.[21]—ED.)

The form of albumin excreted by these patients is, in part, at least, ordinary serum albumin, and, in part, it is in a form

[20] Weidenfeld, Wien. med. Wochens., 1894, Nos. 12 and 14; Ott, Arch. f. klin. Med., vol. liii. p. 604.

[21] Erlanger and Hooker, Johns Hopkins Hosp. Reports, vol. xii.

that is precipitated by acetic acid,—*i.e.*, it is possibly a neucleo-proteid. It is important to determine the exact nature of this proteid, for we might thereby learn something of its origin. There are three possible sources of the albumin in the urine. It is possible, in the first place, that the albumin is excreted because it is of such a character that it cannot be assimilated by the body (see page 431) ; in the second place, it may appear because the renal cells do not hold back the normal proteids of the blood; and in the third place, it may be derived directly from the cells of the kidneys or from the cells of the urinary tract. The fact that what appears to be a nucleo-proteid is present in the urine of these patients is of especial interest, for only rarely is this form of albumin found in the urine of patients with genuine nephritis.

Various views have been expressed as to the relationship between this form of albuminuria and true nephritis. Some have maintained that the two differ only in degree, while others regard the two as fundamentally different.[22] The theory that this " albuminuria of adolescence" is a peculiar form of nephritis is favored by the facts that it is often accompanied by casts in the urine,[23] and that an intermittent albuminuria occurs not infrequently during the course of a chronic nephritis or toward the close of an acute nephritis. Yet these observations do not prove conclusively that we are here dealing with a true nephritis in the ordinary use of the term, and even the presence of casts is of doubtful significance. Of great practical importance is the question as to the prognosis of these forms of albuminuria. So far as I know, it has not been definitely proved that a single case of this form of albuminuria has ever become transformed into a true nephritis. I have observed a number of such cases myself over long periods of

[22] See v. Noorden, in discussion on Klemperer's Paper, Berl. klin. Wochens., 1889, No. 39; v. Leube, Ther. d. Gegenw., October, 1902.

[23] Huger, Johns Hopkins Hosp. Bull., 1902, p. 75.

years, and have yet to see such a transformation, and I am therefore personaly inclined to regard them as relatively harmless. Yet more time must elapse before the prognosis of this form of albuminuria can be definitely settled. (A more serious view of this form of albuminuria is taken by Senator, Caspar, and others.[24]—Ed.).

Albuminuria from Injury to the Renal Cells.—An injury to the secreting cells of the kidneys may cause the proteid constituents of these cells to pass into the urine. Such apparently is the interpretation that must be placed upon the appearance of nucleo-proteids in the urine after certain injuries to the renal parenchyma, such as may be caused by a temporary interference with the blood-supply, or by the toxins of infectious diseases.[25] The finding of nucleo-proteids in the urine in these conditions is of considerable theoretical interest, and it would seem to indicate that the renal cells have been damaged in some special way, for in most cases of ordinary nephritis no nucleo-proteids are excreted.

On the other hand, an injury to the renal cells may lead to albuminuria because it renders them abnormally permeable to the passage of the proteids of the blood. This abnormal permeability must reside either in the renal cells themselves or in the basement membranes, for the walls of the capillaries will allow proteids to pass through normally. The epithelium of the glomeruli appears to be particularly susceptible to agents that increase the permeability in this manner; whereas, the epithelium of the convoluted tubules are thus affected only when the injurious agent is very powerful.[26] It is difficult to judge, however, to what extent the latter have become permeable, for the coagulated proteids often seen in the lumina

[24] Zentr. f. in Med, 1905, p. 67.

[25] Pichler and Vogt, Ztrbl. f. in. Med., 1894, No. 17; Obermayer, Ztrbl. f. in. Med., 1892, No. 1; Kossler, Berl klin Wochens., 1895, No. 14

[26] Ribbert, Nephritis u Albuminuria, Bonn, 1881, Litten, Ztrbl f. d med. Wis., 1880, No. 9.

of these tubules must have come, in part at least, from the glomeruli above.

We do not know the nature of the changes which render the epithelial cells permeable for proteids. In many cases of albuminuria, no anatomical lesions of the kidney are demonstrable,[27] while, on the other hand, granular and even fatty degeneration of the cells may be present without any consequent albuminuria. Some have attached a certain significance to a loss of flagella from the cells of the convoluted tubules, yet it seems improbable that this should be of much importance, for these flagella may also be lost in conditions in which no albuminuria has been present.[28]

Albuminuria from Circulatory Disturbances of the Kidneys.—Circulatory disturbances of the kidneys may lead to albuminuria if the velocity of blood-flow through them sinks below a certain limit. What this limit is, is not definitely known, and it seems to be different in different individuals. The retarded renal circulation may be due to a number of causes, such as obstruction of the renal veins, increase in the general venous pressure, spasm of the renal arteries from lead colic, tetanus, etc., or an increased pressure within the urinary passages, with secondary pressure upon the renal capillaries and veins. It seems probable that the retarded circulation primarily injures the renal cells, either by failing to supply them with sufficient food or by failing to remove properly the waste products derived from their metabolic activities. In confirmation of this view that the primary damage is done to the parenchyma cells, is the fact that the proteids which first appear in the urine after an artificial constriction of the renal vessels are nucleo-proteids, probably derived from the renal cells.[29]

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[27] Litten, Ztft. f. klin. Med., vol. i. p. 131; vol. xxii. p. 182; Ribbert, loc. cit.; Cabot, Jour. of Am. Med. Assoc., 1905, p. 837.

[28] Lorenz, Ztft. f. klin. Med., vol. xv. p. 500.

[29] Pichler and Vogt, Ztrbl. f. in. Med., 1894, No. 17.

Toxic Albuminurias.—It is easy to conceive how poisonous substances, circulating in the blood, might injure the epithelial cells of the kidney and render them permeable to proteids. Such an effect may be produced by metallic poisons, by the balsams, etc., as well as by the more complex bacterial and other toxins. The various albuminurias that occur during infectious diseases,[30] as well as those occurring during pregnancy, belong, for the most part, in this category of toxic albuminurias. It is not a great step from these degenerative processes to the true renal inflammations. In the former only the parenchyma cells are affected, whereas in the latter the blood-vessels and the interstitial tissues are more or less diseased. Many poisons, in small doses, will produce degenerations, and in long continued or very large doses, inflammations; whereas, others seem to cause an inflammation from the start. Why some should thus effect the epithelium primarily and others the interstitial tissue is not known. The poisons that produce these toxic albuminurias are usually formed in the body during acute infectious processes; and, even in the so-called primary forms of nephritis, bacteria have been found in some instances in the urine, thus rendering it probable that the nephritis was of infectious origin.[31]

According to the opinion of experienced clinicians, nephritis may at times develop after exposure to cold, as from a severe wetting or from sleeping upon the ground, but as yet no adequate explanation of the manner in which such a nephritis is caused has been given.

The Varieties of Proteids in the Urine.—Most of the proteids that appear in the urine during renal diseases come from the blood-plasma, though, as we have seen, a small quantity is possibly derived from the renal epithelial cells themselves. No definite relation exists, however, between the relative amounts

[30] Lüthje, Ther. d. Gegenw., November, 1903.
[31] Mannaberg, Ztft. f. klin. Med., vol xviii p. 223.

of the various proteids in the blood and the relative amounts of these same proteids in the urine. Indeed, in some pathological conditions only one kind of proteid is excreted by the kidneys.[32] The difference in the permeability of the kidneys to different proteids apparently depends upon the nature of the epithelial lesion.

Since the investigations from Hofmeister's laboratory have shown that the globulins of the blood are made up of at least two separate substances, interest has arisen as to the amount of these two globulins which appear in the urine in various pathological conditions. In chronic nephritis and especially in chronic interstitial nephritis, only traces of euglobulin may be found in the urine;[33] whereas, in febrile albuminuria, considerable amounts of this globulin may appear in the urine.[34] These globulins are the main causes of certain precipitates that form when acetic acid is added to some pathological urines.[35]

Although the greater portion of the abnormal proteids in the urine may be classified under the group names of albumins and globulins, yet it should be remembered that our chemical methods are still very imperfect so far as the further subdivision of these groups is concerned. Proteids may give precisely the same chemical reactions and yet vary enormously in their physiological properties, and while the one is possibly a normal constituent of the body, and if artificially introduced into the circulation, it will be assimilated and do no harm, another may be very toxic, or, at any rate, it cannot be assimilated and will consequently be excreted in the urine as a useless substance. It is hardly possible to avoid the suspicion that certain proteids appear in the urine, especially during acute

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[32] Werner, Deut. med. Wochens., 1883, No. 40; Calvo, Ztft. f. klin. Med., vol. li. p. 502.

[33] Calvo, loc. cit.

[34] Matsumoto, Arch. f. klin. Med., vol. lxxv. p. 398.

[35] Staehelin, Münch. med. Wochens., 1902, No. 34.

infectious diseases, because they are of an abnormal character
and cannot be assimilated in the body (see page 431).

The Amount of Albumin excreted.—The amount of albu-
min in the urine depends primarily upon the degree and extent
of the injury to the secreting cells, and it is largely independent
of the quantity of urine excreted. In addition it seems to be
influenced by the same factors which produce the so-called
physiological albuminurias,—posture, muscular exertion, etc.

Casts.—The diseased renal epithelium may become perme-
able to the red and white corpuscles of the blood, and these can
then pass into the urine. In addition to these blood-cells and
the desquamated renal cells themselves, pathological urines
often contain casts of the interiors of the uriniferous tubules.
These casts are most frequently composed of a hyaline or gran-
ular material, but they may contain in addition various cells.
The material composing them has been regarded by some
authors as fibrin, and parts of it will often give the Weigert
reaction; yet it is questionable whether this hyaline material
is true fibrin or not. Two theories as to the formation of casts
have been advanced. According to the one, they result from
the coagulation of the constituents of the blood that escape into
the uriniferous tubules; according to the other, they are de-
rived more directly from substances present in the renal cells [36]
Casts often appear in the urine, even when albumin is absent.

The Effect of Changes in the Composition of the Blood.—
The amount of water in the body directly influences the secre-
tion of urine, and it is well known, for example, that he who
drinks much will also urinate much. Indeed, excessive drink-
ing may be the primary cause of certain cases of diabetes
insipidus, for it is possible to cure some of them by merely lim-
iting the quantity of fluids taken by mouth.[37]

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[36] See Torok and Pollak, Arch. f exp. Path. vol xxv p 87; Luthje,
Arch f klin Med, vol lxxiv p 163.

[37] Westphal, Berl klin Wochens., 1889, No. 35.

On the other hand, if the water in the body be diminished, either because the patient drinks but little or because he loses much water by other channels, then the quantity of urine is also diminished. We see such a diminution after excessive sweating, especially in a dry climate, as well as in many diarrhœal disturbances, such as Asiatic cholera. The exact cause of the many variations in the amount of urine, which obviously serve to maintain a constant concentration of the blood, is not known.

Many solid substances also tend to increase the urinary secretion, among which substances are many of the constituents of normal urine. These constituents appear in the urine, not in proportion to their concentration in the blood, but in proportion as they are present there in greater or less concentration than normal. If present in greater amount than normal, they are rapidly excreted; if present in less amount than normal, their excretion is greatly diminished. In this way the kidney tends to maintain the blood at a constant composition, and for this reason, also, the examination of the urine often furnishes the physician with valuable evidence as to the concentration of any particular substance in the blood.

When any solid is being excreted, it tends to carry a certain amount of water along with it into the urine, though the amount of water thus carried out differs for different solids. Advantage is taken of this fact in the use of certain substances as diuretics. We have already described one class of diuretics, —viz., those that increase the secretion of urine by improving the circulation through the kidneys. The substances now under consideration, however, act in a totally different manner, for they will increase the urine even when the circulation and the renal cells are normal. For example, many salts accelerate the flow of urine, apparently because they readily diffuse through the renal membrane and carry a large amount of water

with them. Yet we cannot deny that these salts may exert some direct specific action upon the renal cells,[38] and such a direct action has been definitely proved for certain substances, such as caffeine.[39]

The relation between different concentrations of dextrose in the blood and the appearance of dextrose in the urine has been carefully studied. About 0.1 to 0.2 per cent. of sugar is normally present in the plasma, and only very minute traces are present in the urine. If the concentration in the blood exceeds 0.2 per cent., however, then dextrose appears in the urine in comparatively large quantities. We have already mentioned that such a hyperglycæmia is the cause of the glycosuria of diabetes; and, from the fact that the epithelium of the convoluted tubules undergo glycogenic degeneration in this disease, it seems quite probable that they are the cells which secrete the sugar, and so tend to maintain the dextrose in the blood at a constant concentration.

We have said that normal kidneys hold back the proteids of the blood plasma most carefully. This is not true, however, of all proteids that may happen to be present in the blood. Of the many that have been artificially introduced into the circulation, a small number, such as an egg albumin, casein, and hæmoglobin, immediately pass through into the urine. Even when uncoagulated egg albumin is taken by mouth in large quantities, some will often be excreted by the kidneys. Now, abnormal proteids are certainly formed in the body during some pathological processes, and especially during the infectious diseases, and it seems not improbable that many of the albuminurias present in these conditions are due, not to a primary injury to the renal structures, but to the elimination of abnormal proteids that cannot be assimilated in the body. So,

[38] See, for example, J. B. MacCallum, Jour. of Exp. Zool., vol. i. p. 179.

[39] Schröder, Arch. f. exp. Path., vol. xxii. p. 53.

too, those proteids sometimes found in the urine during leu-kæmia, which are precipitated by the addition of acetic acid, are also possibly excreted because they cannot be assimilated. In fact, such abnormal proteids have been demonstrated in the blood itself.[40]

Albumoses and peptones will also appear in the urine if they be injected into the circulation in sufficiently large quantities. They do not appear normally during digestion, apparently because they are reconverted into more complex proteids in or just behind the intestinal mucosa. Possibly this reconvertion does not take place under certain pathological conditions, and this may explain the albumosurias, occasionally seen in connection with ulcerations of the intestinal wall.[41] In other conditions, as in fever, albumoses are formed during a pathological destruction of the proteids of the body, and here again they may appear in the urine.

Living bacteria may be excreted by the apparently intact kidneys, and so reach the urine. They can certainly pass through the glomeruli in this manner, for micro-organisms have been seen within these structures.

The Effect of Disturbances of the Urinary Secretion upon the Body.—Disease of the kidney may effect the body in at least two ways,—either by allowing substances to pass out which ought to be retained, or by retaining substances which ought to pass out. Of the substances that escape abnormally, albumin is the only one of importance. The actual loss of proteids by this channel is, however, relatively slight, amounting to only a small number of grams a day. It seems quite improbable that this small loss should in itself produce much effect upon the body as a whole, though it cannot be denied that it may affect the composition of the blood to some extent (see).

[40] Obermayer, Ztfbl. f. in. Med., 1892, No. 1.

[41] Schultess, Arch. f. klin. Med., vol. lviii. p. 325; vol. lx. p. 55.

On the other hand, the retention of substances in the body that should normally be excreted apparently leads to a variety of disturbances.

Uræmia.—Not infrequently, during the course of renal disease, a group of symptoms develops which seems to be caused by some sort of an intoxication. This is called uræmia,[42] and it presents the most varied clinical picture. The patient may become stupid or comatose, or, on the other hand, extremely irritable. He may have local or general convulsions, or he may suffer from paralysis of various parts of his body. Sometimes he becomes blind without there being present any objective lesion in the eyes. The heart's action is at first slow and irregular, but later very rapid; the respirations become deeper or assume the Cheyne-Stokes type; finally, there may be vomiting or diarrhœa. These are the most important symptoms of this condition. They occur singly or in groups, and they may develop suddenly or slowly. The greater number of them are evidently due to cerebral disturbances, though, as a rule, no corresponding anatomical lesions are found there.

It has recently been claimed that these many and varied symptoms do not all arise from a common cause,[43] and I am personally inclined to be of this opinion. Yet it is difficult to decide this question, for, as is well known, the same poison may act quite differently upon different individuals, and upon different organs in different individuals, owing to variations in the susceptibility of different persons. As we shall see, furthermore, there are reasons for believing that a number of causes may be operative in the production of uræmia.

[42] See Landois, Die Uræmia, second edition; Bouchard, Leçons sur les autointox., Paris, 1887; Honigmann, in Lubarsch-Ostertag, Ergeb d. allge. Path Physiol.; Ascoli, Vorles. ü. Uræmie, Jena, 1903; Herter, Montreal med. Jour , May, 1898.

[43] Ascoli, loc. cit.

Beyond doubt, the symptoms of uræmia are caused by some sort of an intoxication, and our first supposition would naturally be that this intoxication is due to the retention of substances in the body that should normally be excreted by the kidneys. As a matter of fact, patients in uræmia frequently excrete abnormally small amounts of urine and of urinary solids.[44] Indeed, the excretion of various solids may be diminished even though the quantity of urine be increased. The retention of urinary substances in the body has, furthermore, been directly demonstrated by examinations of the blood. The number of molecules in the plasma is increased during uræmia, for its freezing point is lowered. Since its electrical conductivity is unaltered,[45] however, the increased concentration of the blood cannot be due to an excess of electrolytes, such as salts, but to an excess of organic molecules of some sort.

Yet a number of facts speak against the view that uræmia is caused by the retention of substances that are normally excreted through the kidneys. In the first place, an absolute anuria may persist for days without producing uræmic symptoms, and, furthermore, even though death results from suppression of urine, the associated symptoms do not precisely coincide with those of uræmia. Patients with anuria seem to pass gradually into a coma without any irritative cerebral symptoms, and the uræmic rise in the blood-pressure, the slow pulse, and the characteristic convulsions are all absent.

Furthermore, no well-defined substance has yet been found that is both retained in the body during uræmia and is capable

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[44] Fleischer, Arch. f. klin. Med., vol. xxix. p. 129; v. Noorden and Ritter, Ztft. f. klin. Med., vol. xix. Sup., p. 197; v. Noorden, Path. d. Stoffwechsels, p. 360; Soetbeer, Ztft. f. phys. Chem., vol. xxxv. p. 85; Köhler, Arch. f. klin. Med., vol. lxv. p. 548.

[45] See Bickel, Deut. med. Wochens., 1902, No. 28.

of procuring uræmic symptoms when injected into a normal animal. Many such substances have been described, yet not one has stood the test of time. Urea, for example, is retained in the body during uræmia,[46] yet it is not toxic in these amounts, and a similar retention has continued for days without the appearance of any uræmic symptoms.[47] Some have regarded the potassium salts as toxic agents, yet the quantity of these salts in the blood of uræmic dogs was not found to be increased.[48] The evidence regarding creatin and uric acid in their relation to uræmia is likewise very inconclusive.[49] We may say, in conclusion, therefore, that no well-defined substance is known which will produce uræmia by its retention in the body.

The urine, however, even in health, possesses certain toxic properties, the exact cause of which is at present unknown.[50] The toxic action of the urine is frequently increased in disease, and it is quite possible that in nephritis toxic substances are formed in abnormally large quantities, and that they are not eliminated properly by the kidneys. Yet this is a pure hypothesis, built upon very insecure foundations, for but little reliance can be placed upon inferences as to the toxicity of normal and pathological urines, when the inferences are derived from the effects of injections of the whole urine into animals. Until some definite toxic substance can be isolated, this hypothesis will continue to retain a more or less questionable standing.

Finally, there exists the possibility that uræmia is due, not to a failure on the part of the kidney to eliminate poisonous substances from the body, but to pathological alteration in

[46] Soetbeer, loc. cit.

[47] Fleischer, loc. cit.

[48] v. Limbeck, Arch. f. exp. Path., vol. xxx p. 180.

[49] Landois, loc. cit.; Bouchard, loc. cit.

[50] Bouchard, Autointoxication; see, also, Honigmann, on Uræmia in Lubarsch-Ostertag, vol. viii. p. 549.

some of its metabolic functions. Of these functions, we know comparatively little; yet that the kidney does possess such functions is proved by the well-known fact that the renal cells can form hippuric acid out of benzoic acid and glycocoll.[51] Brown-Sequard [52] has elaborated the theory that the kidney furnishes an internal secretion to the body, and he has attempted to explain uræmia from this stand-point. Various effects are said to follow the injection of renal extracts,[53] and it has been found that substances tending to raise the blood-pressure are present in normal kidneys, and that they are present in especially large quantities in pathological kidneys.[54] Possibly, further work along these suggestive lines will aid us in our understanding of uræmia.

In conclusion, we may say that although a complete suppression of urine is fatal, the symptoms produced are not absolutely identical with those of uræmia. The convulsions, the increased blood-pressure, and the slow pulse, all of which occur so frequently in uræmia, are in all probability caused, not by the retention of normal urinary products, but by some special uræmic toxin. This hypothetical toxin acts especially upon the central nervous system, and here more particularly upon the cerebral cortex and the medullary centres. In either place it may produce a stimulation or a paralysis.

THE URINARY PASSAGES.

Any portion of the urinary passage, from the kidney out to the mouth of the urethra, may be diseased. Diseases of the urinary bladder and of the renal pelves stand in close etiological relation to one another. If, for example, one of the latter is inflamed, the infected urine that flows into the blad-

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[51] Bunge and Schmiederberg, Arch. f. exp. Path., vol. vi. p. 233.

[52] Arch. de Physiol., 1893, p. 778.

[53] Lépine, Revue de méd., vol. ix. p. 514.

[54] Ascoli, loc. cit., chap. x., xi.

der may there cause changes. On the other hand, if the former be the seat of an inflammation, this may easily spread upward through the ureters to the pelves of the kidneys. Pyelitis is most frequently caused by just such an ascending infection, and every long-continued cystitis is a menace to the patient, for it may produce inflammation of the renal pelvis or of the kidney itself. Certain infections, especially tuberculosis, affect the renal pelvis primarily, in which case the infection enters through the kidneys.

Pathological conditions of the urinary bladder may be caused by vesical calculi, by the irritative or infectious character of the urine that comes from the kidneys, or by inflammations in the neighborhood that extend into it by contiguity. More frequently, however, the infectious agent reaches the bladder through the urethra. It is possible that, in some instances, bacteria enters from the anterior urethra, because the sphincters are weakened or paralyzed; but more frequently the micro-organisms are directly introduced by a catheter or some other instrument. Such an introduction of bacteria into the bladder does not necessarily cause an inflammation; for the normal, complete evacuation of this organ protects it to a certain extent against infection. On the other hand, infection is greatly favored by stasis of the urine, and, for this reason, hypertrophy of the prostate gland, strictures in the urethra, vesical calculi, tumors, etc., are all frequently followed by cystitis.

When bacteria develop in the stagnating contents of the bladder, they may cause various urinary decompositions. Of these, none is more frequent than the so-called ammoniacal decomposition, in which a portion of the urea is transformed into ammonium carbonate, and which may be brought about by various bacteria.[55] In other forms of urinary decomposi-

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[55] Leube, Virch. Arch., vol. c. p 540; v. Jaksch, Ztft. f. phys. Chem., vol. v. p. 395.

tion the neutral sulphur in the urine is converted into hydrogen sulphide.[56] The effects of such fermentations are both general and local. The ammonium salts and the hydrogen sulphide may be absorbed through the altered vesical mucous membrane, and produce their general toxic effects. In addition to this, the ammonia directly attacks the bladder mucosa.

Urinary Calculi.—Urinary calculi may be composed of various compounds, such as uric acid, the urates, calcium oxalate, cystin, the carbonates and phosphates of the alkaline earths, etc. In addition to one or more of these, the calculus always contains a framework that is composed of a proteid-like substance, and this framework is often so intimately mixed with the salts present that chemical methods are necessary to distinguish them. Some stones are of uniform structure throughout, while others show a more or less concentric arrangement, owing to the fact that layers of one substance alternate with layers of another.

An organic framework is present not alone in formed urinary calculi, but in urinary crystals of every description.[57] This fact is of considerable theoretical interest; and, whereas, it was formerly supposed that the organic framework was pathological and was a necessary condition for the formation of calculi, it is now regarded as a physiological structure and comparatively harmless. The material out of which this framework is composed is apparently present in every urine, and it is precipitated along with the precipitation of the inorganic salts. No special explanation of the presence of this organic framework in urinary calculi is therefore necessary.

(*a*) *Uric Acid and Urate Calculi.*—The calculi most frequently found in the bladder are composed of uric acid or of

[56] F. Müller, Berl. klin. Wochens., 1887, Nos. 23 and 24.

[57] Moritz, Kongr. f. in. Med., 1896, p. 523.

the urates. Uric acid stones are often formed in the kidneys themselves and apparently even during the earliest periods of life. As is well known, uric acid deposits are frequently present in the uriniferous tubules of the fœtus and of the new-born infant, forming the so-called uric acid infarcts. For our present purposes it is immaterial whether the uric acid in these cases is excreted in excessive amounts or whether it is merely precipitated with unusual ease; for the formation of calculi depends primarily upon the precipitation of salts. Apparently these renal deposits in new-born infants are normally washed out of the kidneys and out of the urinary passages without causing any symptoms. Possibly, however, these infarcts stand in some close causal relation to the formation of uric acid stones in childhood.

Since the formation of calculi depends primarily upon the precipitation of the uric acid out of the urine, two factors are of importance in their formation, first, the amount of uric acid secreted, and secondly, the ability of the urine to hold this in solution. Of these, the latter factor is the more important and the more variable. Urine dissolves far more uric acid than does pure water.[58] Normally the uric acid is present in the urine mainly as a mono-sodium salt. The mono-sodium phosphate of the urine, however, tends to take the sodium away from the monourate, forming a di-sodium phosphate and leaving free uric acid, which latter is comparatively insoluble. The presence of free carbonic acid in the urine tends to hold uric acid in solution.[59] It is furthermore quite possible that uric acid is often held in solution in the urine as some special combination. We know, for example, that the quantity of urea in the urine affects the solubility of uric acid,[60] and it is probable that other organic substances will do the same. Uric

[58] Bunge, Physiol. Chem., third edition, p. 308.
[59] G. Klemperer, Ztft. f. phys. Ther., vol. iv p. 48.
[60] Rüdel, Arch. f. exp Path., vol. xxx. p. 469.

acid calculi are often associated with gout, the two being grouped together under the name of the uric acid diathesis. We have already seen that the uric acid within the body is probably held in solution in organic combinations (page 373), and the same may be equally true concerning the urine. We may say, therefore, in conclusion, that the precipitation of uric acid out of the urine depends upon numerous factors, and that the presence or absence of other substances probably plays a more important rôle than does the mere quantity of the acid itself.

(b) *Oxalate Calculi.*—The solution of calcium oxalate in the urine is greatly favored by an acid reaction. If this latter be reduced from any cause, the mono-sodium phosphate tends to be converted into di-sodium phosphate, and the precipitation of calcium oxalate is favored; yet this appears to be only one factor in the process.[61]

(c) *Phosphatic Calculi.*—The phosphates of the alkaline earths are soluble in the urine mainly as mono- or di-phosphatic salts, and they tend to be precipitated when the reaction of the urine becomes alkaline and normal phosphates are formed. Ammonium-magnesium-phosphate is also formed under these circumstances.

These phosphatic calculi are formed almost exclusively in the bladder, but they frequently precipitate about a nucleus composed of some other material, such as a uric acid stone or some foreign body that has been artificially introduced into the bladder. Their formation is greatly favored by stagnation of urine, and, as a consequence, they occur most frequently in association with cystitis; for this, as we have shown, is itself favored by stagnation, and is frequently accompanied by an alkaline reaction of the urine, owing to the associated ammoniacal fermentation. •

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[61] G. Klemperer, Berl. klin. Wochens., 1901, p. 1289; Klemperer and Tritschler, Ztft. f. klin. Med., vol. xliv. p. 337.

(d) *Cystin and Xanthin* calculi are extremely rare. The former is a substance containing sulphur, and is derived from proteid sources. It appears to be formed by certain little understood bacterial decompositions in the intestines. Apparently, it never occurs in normal urine. Xanthin is present even in normal urine in small amounts, but the cause of its precipitation is not understood.

The Symptoms of Urinary Calculi.—The hard, uneven stones, especially the uric acid or calcium oxalate calculi, irritate the mucous membrane of the urinary tract and cause inflammations, pain, and hemorrhages. If the calculus obstruct a ureter, then attacks of renal colic, with severe pains and vomiting, may follow. If the occlusion persists for a long period of time, then hydronephrosis and the other sequelæ of urinary retention are likely to develop.

Vesical calculi may suddenly stop the flow of urine by dropping before the mouth of the urethra. This gives rise to vesical tenesmus, which is not, however, a pathognomonic symptom of calculi, but may be produced by inflammations of the neck of the bladder or by vesical tumors. The symptoms of vesical tenesmus are very similar to those of tenesmus of the rectum. The irritation of the neck of the bladder causes a frequent desire to urinate and the bladder consequently contracts frequently and forcibly, and this causes considerable pain; yet, on account of the small amount of urine present, but little can be voided.

The Origin of Pain in the Urinary Passages.—A diseased kidney may cause pain, or, at any rate, a dull feeling of pressure in the lumbar region. This is not infrequently observed in association with acute or chronic nephritis. More severe pains are usually due to affections of the lower urinary passages, and, as a rule, they are caused by a spasm of the smooth muscle lining the urinary tract. These spasms are caused by reflexes from the mucous membrane, which originate either

from the irritation produced by a foreign body or from inflammatory or ulcerative processes in the mucous membrane itself. The muscular spasm in these cases is comparable to that which gives rise to biliary or intestinal colic. Apparently, the mucous membrane possesses nerves of sensation and the direct irritation of these may also cause certain unpleasant sensations.

CHAPTER XII.

THE NERVOUS SYSTEM.

THE activities of the nervous system give rise to two classes of phenomena, those pertaining to the body and those pertaining to the mind. We do not propose to consider the latter, nor even to discuss the relationship that exists between the body and the mind. This question involves some of the deepest problems concerning life, and psychiatry must assist psychology in their solution; for in this as in other fields of medicine, our knowledge of the normal physiological processes becomes broader and more accurate when we study the pathological variations that these processes may undergo. In the present chapter we propose to limit our discussion, in a general way, to those disturbances of the nervous system which do not affect the mind, even though this division is an artificial one and cannot be carried out strictly and consistently.

The nervous symptoms that we propose to consider may be divided into two main groups. Those in the first group are called focal symptoms, because they are caused by pathological changes involving certain limited portions of the nervous system. Those in the second group are called general symptoms because the agent that causes them affects the nervous system as a whole. Of these general symptoms, some evidently proceed from certain definite localities, whereas the origin of many others cannot be traced. The same general injurious agent may act upon all parts of the nervous system, yet it affects certain portions more than others, because the former happen to be more vulnerable to the particular agent in question.

Disturbances of the Circulation.—The central nervous

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system must receive a sufficient supply of blood in order to function properly. Some of the symptoms that result from circulatory disturbances have already been mentioned in the chapter on respiration. We spoke there of the extraordinary sensitiveness of the respiratory centre to any change in the quantity or quality of the blood that comes to it, as well as of the effects of such changes upon other medullary centres. The cerebral cortex is not affected until some time after the medulla, at which time the consciousness becomes clouded and the horrible sense of suffocation is diminished or lost. Although the brain is ordinarily extremely sensitive to circulatory changes, it often appears as if it can accommodate itself to an insufficient blood supply in chronic circulatory derangements. It is extremely difficult, however, to form an accurate judgment on this question, for we have no method for measuring the circulatory disturbances in the brain; yet it is often truly astonishing to see what little effect the most pronounced chronic venous stasis or the most marked arterial anæmia produces upon the cerebral functions.

The temporary loss of consciousness known as fainting is usually due to an acute cerebral anæmia. It may occur in strong and otherwise healthy individuals, but it is much more frequent in anæmic girls or in older individuals with degenerations of the cerebral arteries. During the fainting spell the patient loses consciousness, falls, and lies for a time, breathing quietly, but with a pale, non-cyanosed face. Finally, after a while, he gradually recovers. Although the cerebrum has ceased to act, the medulla appears to perform its functions quite normally, just as it does during light narcosis. It seems improbable, therefore, that the disturbance of circulation in fainting affects all parts of the brain equally; for if this were so, we should expect more medullary symptoms. We know that localized anæmias frequently occur in other parts of the body, and that, in arteriosclerosis, such circumscribed circula-

tory derangements are particularly frequent; and it seems quite possible that the anæmia causing the syncope affects only a part of the brain, as could happen, for example, if certain vessels became narrowed either by a spasm or by a relative thickening of their walls.

Other anæmic manifestations of nervous origin are more difficult to explain. Some, such as headache, ringing in the ears, spots before the eyes, and dizziness, appear to be irritative in character; while others, such as the common feeling of lassitude, are depressive. These symptoms are often ascribed directly to a cerebral anæmia which either diminishes the oxygen supply to the brain or affects its nutrition in some other way; but these suppositions have not yet been definitely proved. There are many other possibilities. Chemical substances, resulting from pathological alterations of the general metabolism, may poison the brain in some manner, and it is even possible that the symptoms do not originate in the brain at all, but in the peripheral sense organs. Finally, Lenhartz [1] has shown that the headache and dizziness of chlorosis are associated with an increase in the subarachnoid pressure. It is apparent, therefore, that the general nervous symptoms of anæmia may arise from a variety of causes.

The Cerebrospinal Lymphatic System.—The brain and spinal cord are suspended in a fluid that is constantly changing through the processes of secretion and absorption. We need not describe the many advantages of this mechanism; how it acts as a cushion about the delicate nervous structures when the body is jarred, nor how the brain is protected from rapid alterations in arterial pressure by the layer of lymphatic fluid that circles each of its blood-vessels.

Most observers have found the pressure of the cerebrospinal fluid to be normally rather low, although it apparently differs considerably in different individuals. Its height depends

[1] Münch. med. Wochens, 1896, Nos. 8 and 9.

in part upon the general blood-pressure, but mainly upon the relation that exists between the secretion and the absorption of the lymph. The characteristic composition of this cerebrospinal fluid—viz., a low percentage of albumin and a high percentage of potassium salts—shows that it is not an ordinary transudate, but a secretory product from certain cells, probably those of the choroid plexuses.[2] The resorption of this fluid takes place mainly in the Pacchionian corpuscles and to a lesser extent in the lymphatics of the nose and neck.

Increased Cerebral Pressure.—The pressure of the cerebrospinal fluid may be pathologically increased to varying degrees and by different causes. For example, tumors may bring this about merely because they take up space within the cranial cavity, though they are especially liable to do so when they press upon the veins of Galen and thus impede the outflow of venous blood. Intracranial hemorrhages may also increase the cerebrospinal pressure.

If the cranial cavity becomes crowded from any cause, the brain substance cannot be compressed into a smaller space, for the nervous tissue is practically incompressible.[8] A certain relief is afforded, however, by the escape of cerebrospinal fluid into those portions of the dura mater that are comparatively distensible, such as is the dura of the cord. A new equilibrium of pressure is then established. What the new pressure will be depends upon the size of the compressing agent, the distensibility of the dura, and, finally, upon the relation that exists between the secretion and absorption of cerebrospinal fluid. It is apparent that when so many factors enter into the final result the same cause may produce quite different effects in different individuals.

From these considerations it would appear that, when a hard body is added to the contents of the skull, the increase in

[2] Falkenheim and Naunyn, Arch. f. exp. Path., vol. xxii. p. 269.

[8] Grashey, Allgem. Ztft. f. Psych., vol. xliii. p. 267.

pressure would be roughly proportionate to the size of the "foreign body," and that the space taken up by smaller bodies could be fairly well compensated for by the escape of lymph from the cranial cavity. In certain cases, however, especially in certain brain tumors, no such definite relation seems to exist between the size of the tumor and the increase in the cerebrospinal pressure. The smallest tumor may cause a tremendous rise in pressure. Furthermore, if some of the cerebrospinal fluid be drawn off in order to relieve the pressure, it will frequently re-collect with great rapidity. These facts do not accord with the view that brain tumors increase the cerebral pressure solely by their mechanical action. It would seem rather as if the production or the absorption of the cerebrospinal fluid were directly affected. Possibly the conditions present are analogous to those that exist in tumors of the pleura or of the peritoneum; *i.e.*, some sort of an inflammatory process is taking place in the arachnoid. In favor of this view are the facts that the cerebrospinal fluid of these patients often contains more albumin than normally, and that the accompanying choked disk is almost certainly of an inflammatory nature.

The increased cerebral pressure that accompanies meningitis is caused by a disturbance in the balance between the production and absorption of cerebrospinal fluid. It seems probable, indeed, that both the production is increased and the absorption diminished in this condition.

The chronic hydrocephalus of children is characterized by a large collection of cerebrospinal fluid, but its cause is not well understood. Perhaps a mild inflammatory process is present (ependymitis); though this seems improbable in most cases, from the fact that the percentage of albumin in the fluid is not increased. Chlorotic girls frequently show an increased cerebral pressure, yet here again the cause is very uncertain. The mild optic neuritis often seen in these patients [4]

[4] Romberg, Berl klin. Wochens., 1897, No. 25.

may possibly be produced by the increased cerebral pressure, though it seems more probable that it results directly from the poor condition of the blood.

When the pressure of the cerebrospinal fluid is increased from any of these causes, certain symptoms usually follow, among which are headache, general bodily and psychic weakness, and characteristic alterations in the fundus of the eyes, the so-called choked disks. These have been termed the symptoms of latent cerebral pressure, and they are supposed to be caused by the tissue changes that follow the increased pressure in the cranial cavity. They depend less upon the height than upon the duration of the increased pressure.[5] It would be interesting to know what the minimum pressure is that can produce a choked disk, but the data at our disposal do not suffice to determine this.[6]

Although choked disk is one of the most important clinical signs of increased cerebral pressure, the manner in which it is produced is still very uncertain. According to the opinion of most ophthalmologists, a mere increase in the intracranial pressure does not suffice to cause it, and other factors must be present. Anatomically, it usually appears to be a true inflammation, involving both the nerve and the neighboring retina.[7] The optic papilla is swollen, and there is an associated œdema and venous stasis, but we do not know whether the œdema and stasis ordinarily develop before the inflammation or not. That stasis alone should cause the inflammation is contrary to all our pathological experience with œdema in other parts of the body. It is quite possible that some inflam-

[5] Falkenheim and Naunyn, Arch. f. exp. Path., vol. xxii. p. 301.

[6] See Lehnhartz, Münch. med. Wochens., 1896, Nos. 8 and 9; Stadlemann, Grenzgebeite, vol. ii. p. 549.

[7] This is not an invariable rule, however, for Krückmann has stated in a letter to the author that he has recently seen a choked disk that presented none of the classical signs of inflammation, this observation being confirmed by Marchand.

matory irritant, produced by the changes within the brain, acts upon the retina. According to this view, two factors contribute to the causation of choked disk; first, an increase in the pressure of the fluid within the optic sheath; and secondly, some unknown inflammatory agent. This hypothesis would explain many peculiar cases in which a choked disk is absent even though the intracranial pressure is high, as happens in some cases of hydrocephalus. It would appear that the inflammatory factor is here absent.

If the pressure of the cerebrospinal fluid be still further increased, a second series of phenomena develop, the so-called direct or manifest symptoms of cerebral pressure. The essential causes of these is a disturbance of the cerebral circulation. We have already described the peculiar conditions that govern the intracranial pressure and how space may be made for foreign bodies by an escape of lymph. When, in spite of this compensatory mechanism, the pressure attains a certain height, those parts of the vascular system that can be compressed most easily—*i.e.*, the veins just before their entrance into the rigid sinuses—become narrowed or even closed. The resulting stasis of blood increases the pressure in the corresponding capillaries and the veins are then opened again, so that they alternately open and close, or, as Grashey says, they vibrate. It is not certain what cerebral manifestations accompany this phenomenon. From experimental data, it would appear that the really characteristic symptoms of cerebral compression only begin at about the time when the intracranial pressure becomes sufficient to compress the arteries. It is about at this time that we have the characteristic stupor, the vomiting, the slowing of the pulse and the respirations, and finally the general epileptiform convulsions. The primary cause of these symptoms seems to be an arterial anæmia that occurs because the subarachnoid pressure is greater than the arterial pressure. It is therefore theoretically possible that these symptoms could

be produced either by a rise in the subarachnoid pressure or by a fall in the arterial pressure. When the nervous symptoms of increased cerebral pressure have once become established, they may continue for some time, even though the intracranial pressure lessens, for the reason that less force is required to hold the vessels closed than to compress them originally.

The absolute amount of cerebral pressure necessary to produce these direct symptoms is therefore rather indefinite, and it often happens that during the course of indirect symptoms, the direct ones will appear and again disappear, apparently on account of circulatory disturbances.

(It is a well-recognized fact that, if the space in the cranial cavity be rapidly encroached upon by any cause, the general blood-pressure is increased. Experiments upon dogs would seem to indicate that this rise in the blood-pressure is a purposeful reaction, and that it serves to keep the pressure within the arterioles and capillaries of the medulla at a higher level than is the extravascular pressure at this point. In this manner, a fatal bulbar anæmia, which would otherwise result from the rise of intracranial pressure, is warded off.[8] A similar rise of blood-pressure has been demonstrated after cerebral hemorrhages in man, the extent of the rise being a measure of the amount of compression exerted upon the medulla.[9]

At the height of the acute compression, rhythmical breathing of the Cheyne-Stokes type, rhythmic alterations in the size of the pupils, and rhythmic changes in the depth of stupor may all occur. These seem to be caused by the varying relations between the intracranial and the arterial pressure.

A final stage of acute cerebral compression has been described, the so-called stage of paralysis, in which the vasomotor centre is no longer able to maintain the arterial pressure

[8] Cushing, Mitth. aus der Grenzgeb., vol. ix. p. 773; Am. Jour. of the Med. Sci., 1902, vol. lxxiv. p. 375.

[9] Cushing, Am. Jour. of the Med. Sci., June, 1903.

above that in the cranial cavity. The blood-pressure then falls rapidly, the heart action and the respirations become irregular, the muscles relax, and the deepening coma ends in death.—Ed.)

Cerebral Concussion.—The symptoms of cerebral concussion differ considerably from those of compression. The pale, unconscious patient lies with relaxed muscles and with weak respirations. His pulse is soft and small, its rate being either increased or diminished. His pupils are often immobile, and vomiting frequently occurs. Indeed, he might be thought to be suffering from a fainting spell.

Cerebral concussion is ordinarily produced by a violent blow upon the head or upon some other part of the body, yet no definite relation seems to exist between the force of the blow and the severity of the symptoms, and even serious cerebral injuries may be produced by violence without there being present any of the typical symptoms of concussion. The symptoms of concussion are essentially those of cerebral inactivity, reaching different grades in different cases. In the milder form of concussion, the cerebral cortex alone is affected (unconsciousness), in the more severe forms the medullary centres become involved (respiratory and circulatory disturbances), while in the most severe the vital functions are suspended.

No definite anatomical changes in the brain, common to all cases of concussion, have been found. The symptoms can hardly be due to circulatory disturbances, for they have been produced on bloodless frogs.[10] It seems quite probable that they are produced by injuries to the finer connections between the nerve-cells in the brain, and we know that very severe concussions may even produce slight but demonstrable lesions in the central nervous system.[11]

[10] Koch and Filehne, Arch f. klin Chir., vol. xvii. p. 190.
[11] Schmaus, Virch. Arch, vol cxxii. pp. 326, 470; Kirchgässer, Ztft. f. Nervenheilk, vol. xi. p. 406; vol. xiii. p. 422.

Disturbances of Motility.—The direct motor impulses travel from the cerebrum to the muscles through two sets of fibres. Of these, the first begin in the ganglion cells of the cortical motor area and pass by way of the pyramidal tracts to the anterior horn cells of the spinal cord, or to the corresponding nuclei of the pons or medulla. The terminal fibres of these upper neurons are believed by many to merely touch the lower ganglion cells, by others they are believed to be continuous with them.[12] The second or lower set of neurons begin in the large motor cells of the cord and medulla, and extend thence to the peripheral muscles. The voluntary nervous impulse proceeding to the muscles may be interfered with at any point along this long course with a resulting loss of muscular function. Disturbances of motility may arise, however, from other causes, such as lesions of the muscles, bones, and joints, on the one hand, and from lesions of those parts of the nervous apparatus that assist in co-ordinating the movements or that furnish the will power, on the other.

Some hold that the voluntary motor impulses pass through the cerebellum. However this may be, diseases of the cerebellum certainly do influence our voluntary movements,[13] independently of their effect upon our sense of equilibrium. The innervation of muscles is greatly affected by the centripetal impulses that go from them to the brain. These centripetal impulses pass through the cerebellum so that cerebellar disease at times gives rise to typical ataxia, without there being necessarily any disturbances of cutaneous sensation. Since the fibres from the cerebellum to the cerebrum undergo decussation, and since the impulses from the cerebrum to the muscles again cross the median line, a unilateral lesion of the cerebellum will interfere with the movements of the muscles on the

[12] Bethe, Allgem. Anat. f. Path. d. Nervensystem, Leipzig, 1903.

[13] Mann, Monatschr. f. Phys. u. Neur., vol. xii. p. 280; Bruns, Berl. klin. Wochens., 1900, Nos. 25 and 26.

corresponding side of the body, and this interference may be so marked as to cause a true cerebellar hemiplegia.

If a person is unable to move a certain group of muscles, we speak of it as a paralysis. If the strength of the movement is merely weakened, we speak of it as a paresis. Finally, if the movements are uncertain and irregular, so that a desired movement cannot be accurately carried out, we speak of it as an ataxia.

(*a*) "*Psychical Paralyses.*"—This class comprises many of the motor disturbances that occur in insane patients, especially during stupor, as well as many of the hysterical paralyses. It hardly lies within the province of this book to discuss the nature of these cases, although the subject is an extremely interesting one. It would be necessary to consider the nature of the will and the relation that sensations, conceptions, and memory bear to it, and then, finally, to consider the manner in which these relations may be disturbed in the various pathological conditions under consideration.[14]

Such "psychical paralyses" are characterized, clinically, mainly by their distribution. We do not will a single muscle to contract, but we will a certain movement to take place, which movement ordinarily involves the use of numerous muscles. Correspondingly, the paralyses now under consideration do not affect single muscles, but they involve whole extremities or the execution of certain movements. For example, a patient may be able to move his legs in every direction without any incoördination, and yet he may be unable to walk. Or he may be able to execute all ordinary movements with his hand, but yet be unable to write.

(*b*) *From Lesions of the Motor Tracts.*—The ganglion cells of the upper motor neurons are situated in the so-called motor area of the cerebral cortex, and the symptoms that

[14] See Mobius, Ztrbl. f Nervenh., vol xi p. 3; Biswanger, in the Nothnagel System; Krehl, Volkmann's Vortr, N. F, No. 330.

result from an injury to this part of the brain depends upon the portion of the motor area that is affected. The axis cylinders of these cells may be injured at any point between their origin and their final termination about the large motor cells of the cord or medulla. The effect of an injury to this motor tract depends, both upon which nerve-fibres are injured and upon the severity of the injury. The motor fibres seem to be more susceptible to pressure and stretching than are the sensory fibres. Injuries to this upper tract are caused most commonly by tumors, inflammations, and hemorrhages. The ganglion cells in the cord or their processes in the nerves may be affected by metallic poisons, such as lead, by the action of micro-organisms or toxins, as in meningitis, myelitis, and neuritis, or finally by disturbances of the blood-supply.

(c) *From Lesions of the Muscles.*—Diseases of the muscles naturally interfere with their functional capabilities, as examples of which we may mention the muscular disability which accompanies the dystrophies, trichinosis, polymyositis, and the parenchymatous degenerations that follow some acute infectious diseases.

(d) *From Vascular Disturbances.*—Disturbances of the blood-supply to muscles may also interfere with their capabilities. Veterinarians have long known that arterial disease in the legs of horses seriously interferes with their powers of locomotion. The same is true of man, and the resulting " intermittent claudication" is apparently much more frequent than is generally supposed.[15] If the arteries supplying an extremity become very narrow, the quantity of blood that reaches this extremity may be sufficient to meet all ordinary needs, but at the same time it may be insufficient for any extraordinary demands. · When the patient walks, therefore, the increased demands of the muscles for fresh blood cannot be

[15] Erb, Ztft. f. Nervenheilk., vol. xiii. p. 1; Münch. med. Wochens., 1904, p. 905.

supplied, and, after a certain distance, the leg becomes fatigued and painful, so that the patient can walk no farther. If he rests, however, the power gradually returns and the pains leave his legs, because the supply of blood is now again sufficient. These characteristic symptoms of intermittent claudication are usually associated with definite anatomical alterations in the vessels of the affected extremities, which alterations usually consist in an obliterating endarteritis. Not infrequently these vascular changes eventually lead to gangrene. Apparently a similar intermittent disturbance of function may also be caused by a functional, spasmodic narrowing of the arteries from nervous causes.[16] The parallelism between intermittent claudication and angina pectoris is, therefore, rather striking, for both are usually associated with arteriosclerosis, but both may apparently be caused by a nervous spasm of the corresponding arteries.

(e) *Myotonia Congenita.*—The members of certain families, from youth on, are unable to relax their muscles normally after contraction, because the muscle remains in a sort of tetanus This rigidity is most pronounced after a period of rest, but, as a rule, it lessens after each repetition of the movement. The muscles themselves are usually quite strong, even more so than normally. We may infer that the cause of the disability is located in the muscle itself, for its reaction to the electric current is abnormal (Erb's myotonic reaction), and its anatomical structure is also considerably altered.[17]

(f) *Asthenic Bulbar Paralysis.*[18]—This disease is characterized clinically by the ease with which certain muscles become fatigued after comparatively slight exertion. This fatigue occurs after voluntary use of the muscles, as well as after

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[16] Oppenheim, Ztft. f. Nervenheilk., vol xvii p. 317.

[17] Erb, Die Thomsensche Krankheit., 1886

[18] Jolly, Berl. klin. Wochens., 1895, No. 1 , Strumpell, Ztft. f. Nervenh., vol. viii. p. 16.

stimulation by the electric current, but the ease with which the fatigue develops seems to vary from time to time. Certain muscles, especially those supplied from the medulla, tend especially to be affected. This disease affects the motor apparatus, yet the exact point affected is not known, for anatomical investigations have thus far failed to show any lesion.[19]

Disturbances of Co-ordination.[20]—Before we proceed to the discussion of disturbances of co-ordination, it is first necessary to consider the mechanism whereby we normally govern our movements, so that they shall be executed in a precise and exact manner. The consideration of the normal mechanism of co-ordination presents certain difficulties, however, for we are not certain that it is the same in every case. The adult executes many movements at will, whereas there are others that he learns only by practice. Of the latter, some, such as piano-playing, are learned only by certain individuals, while others, such as walking, speaking, and writing, are learned by all men; such learning being facilitated, doubtlessly, by the fact that our forefathers have practised these movements for generations. There is a gradual transition from the movements that must be learned to the purely voluntary movements, and from these voluntary movements again there is a gradual transition to the purely involuntary movements. To this second transitory class belong those movements of a reflex or automatic type, such as breathing and suckling, that are executed from birth on. As an illustration of the difficulty encountered in attempting to separate these different classes of movements, we may cite the fact that, while swimming must be learned by man, many animals can swim when they first enter the water.

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[19] Strümpell, Ztft. f. Nervenh., vol. viii. p. 16.

[20] Frenkel, Die Behandlung des tabetischen Ataxie, Leipzig, 1900, translated into English by Freyberger; Förster, Die Physiol. u. Path. d. Koördination, Jena, 1902.

There are, therefore, all grades of transition, from the pure reflex movements to the most complex volitional acts. Indeed, the transition occurs many times in the life of a single individual, for movements that were once learned only with the utmost attention and volition are ultimately executed almost unconsciously, merely by willing to do them. At first, these complex acts are carried out under the conscious guidance of all our senses, particularly those of sight, touch, position, etc., but by practice they come to be executed without the individual constituent movements of the act coming to our consciousness.

We know something about the nervous mechanism that underlies these complex practised movements and the more complicated reflexes. These movements may be set in motion voluntarily, or by nervous impulses from the periphery, or, finally, by little-understood internal chemical changes. Since the resulting movements are varied more or less to suit the occasion, it seems improbable that they should be guided by a completely developed mechanism lying within the central nervous system. It would appear rather as if they were guided by impulses from the periphery, which supposition receives strong support from the experiments that have been performed on frogs, dogs, and monkeys.[21] If the posterior nerve-roots in these animals be cut,—i.e., if the sensory impulses from the periphery be eliminated,—not only the complicated reflexes, but the more complex practised movements, such as jumping and running, can no longer be carried out as the animal wills, with exactness and precision. Some muscles contract too strongly, others too feebly, and still others at the wrong time, so that the resulting movement, as a whole, loses its precision, and the picture is very similar to that seen in certain nervous diseases that occur in man, especially tabes.

Since an electrical stimulation of the motor region of the

[21] H. E. Hering, Arch. f. exp. Path., vol. xxxviii p. 266; Neurol. Centralbl., 1897, No. 23; Prag. med. Wochens., 1896.

cerebral cortex gives rise to movements, not of individual muscles, but of co-ordinated groups of muscles, we are led to infer that, in the cortex, movements and not individual muscles are represented.[22] A further grouping of muscles for the execution of certain movements occurs in the anterior horn cells of the spinal cord and in the root-fibres. It is quite certain, therefore, that a certain degree of co-ordination is derived from this arrangement of the cells in the motor nervous system, though, as we have seen, this grouping is not sufficient for complex acts. For these, we depend more or less upon peripheral sensory impulses. We may or we may not be conscious of these impulses, and even when we are not conscious of them, they may yet be utilized by the lower centres in the mechanism of co-ordination. These two forms of sensation, conscious and unconscious, cannot be strictly separated from each other, for our consciousness of them depends largely upon the attention that we direct to them.

Many varieties of sensation may affect our movements. Of these, we may name the senses of sight and of hearing, those of pressure upon the skin, muscles, tendons, and joints, and, finally, the senses of position and of motion. Some of these are of greater importance than are others, and we have seen, for example, that the senses of sight and of hearing are alone inadequate in the monkey and the dog to maintain co-ordination during such complex movements as jumping and running.

Of the sensations mentioned, the most important in the co-ordination of voluntary movements are those derived from the tendons, the joints, and the eyes.[23] If the two former are affected in the first interphalangeal joints, for example, then even such simple movements as the flexion and extension of the fingers may become ataxic. In addition to these sensations

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[22] Beevor and Horsley, Philosoph. Trans., vol. clxxxi. p. 129.

[23] Goldscheider, Ztft. f. klin. Med., vol. xv. p. 82.

from the joints, tendons, and eyes, others from the muscles may also play a considerable rôle in governing our movements.

While the grouping of muscles according to their use in the motor nervous apparatus may therefore furnish a rough sort of co-ordination, this is insufficient for the finer movements. For their execution, centripetal impulses from the periphery are necessary in order to control the time at which the individual muscles shall begin their contractions, the force with which they shall contract, and the time during which they shall remain contracted. .

After this preliminary discussion of the theory of ataxia, it remains to inquire to what extent disturbances of sensation have been actually found in patients who suffer from ataxia,— i.e., from an inability to carry out movements in a precise and accurate manner. It is quite certain that ataxia may occur without there being any demonstrable diminution in the cutaneous senses of pressure, temperature, or pain.[24] On the other hand, it has not been proved that ataxia ever occurs independently of all sensory disturbances, and the earlier cases that were believed to prove this were not sufficiently investigated as to the finer losses of sensation in the joints and muscles.[25] Frenkel, in studying one hundred and fifty cases of tabes, failed to find a single instance of ataxia unaccompanied by sensory changes, these being mainly in the joints and muscles.[26] We may say, therefore, that the main cause of tabetic ataxia is a deficiency in the impulses proceeding from the joints and muscles. That this deficiency may be to a certain extent compensated for in other ways, is shown by the reliance which ataxic individuals place upon their visual impressions. Possibly the absent reflexes, as well as the diminution in muscular

[24] Friedreich, Virch., vol. lxviii. p. 168.
[25] See Erb, Neurol. Ztrbl., 1895, No. 2; Vierordt, Berl. klin. Wochens., 1886, No. 21.
[26] Neurol. Ztrbl., 1897, Nos. 15 and 16.

tonus, also play a not inconsiderable part in the motor disturbances of tabetics.[27]

We now come to the question as to the effect exercised by known disturbances of sensation upon co-ordination. In other words, do such disturbances necessarily lead to ataxia? Many young, apparently hysterical persons have been observed who have shown extensive anæsthesias of the skin and of the deeper structures, without, however, exhibiting any true ataxia.[28] When they kept their eyes open, their movements were perfectly normal,·which, as we have seen, is not the case when, experimentally, all sensory impulses from an extremity are cut off. If these patients closed their eyes, their voluntary movements were, indeed, somewhat abnormal, but no true ataxia was present. To my mind, however, it is necessary to be very cautious in our interpretation of these observations, because the sensory disturbances were apparently of an hysterical character. Hysterical disturbances of sensation unquestionably have their seat in the most central part of the nervous system; in the mind itself, so to speak; and even though these patients are not conscious of their sensations, the latter may certainly be utilized by the lower centres for co-ordination. In no other way can we explain the fact that an hysterical girl, with absolute insensibility of her hands, is able to execute the most delicate hand-work. Indeed, many hysterical patients do not know that they have anæsthesias, mainly because the latter do not cause any motor disturbances. It seems probable, therefore, that in the cases cited at the beginning of this paragraph the ataxia was absent, because the patients unconsciously utilized the centripetal impulses coming from the extremities.

Investigations on other forms of complete lack of sensation are so few that it is impossible to render a final verdict

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[27] See Frenkel, Neurol. Ztrbl., 1896, No. 8.

[28] Strümpell, Arch. f. klin. Med., vol. xxii. p. 332; Heyne, ibid., vol. xlvii. p. 75; v. Ziemssen, ibid., p. 89.

concerning the effect that these produce upon co-ordination. Strümpell, however, has recently published a case in which a complete absence of sensation in the right arm affected the movements most seriously. So long as the patient's eyes were kept open, the ataxia was comparatively slight, but, as soon as they were closed, the incoördination became extreme.[29]

We have shown that centripetal sensory impulses are absolutely necessary for a proper co-ordination of any complex act. The lesion that produces the incoördination, however, does not necessarily lie in the peripheral tracts, but it may be so situated in the central nervous system that it hinders, in some manner, the transmission of impulses across this system, as has been shown in a number of cases.[30] Ataxias may, therefore, be due to different causes, and the resulting clinical picture is not always the same. When we speak of ataxia in general, we usually refer to the tabetic type, for that is the most common and the best understood form. In this form the ataxia is always accompanied by demonstrable sensory changes.

If, from any cause, our movements become more or less incoördinated, then we attempt to compensate for the loss of peripheral control by directing them through the higher centres, very much as does one who is trying for the first time to execute a difficult movement. The movement, thus directed, is usually performed more slowly and less accurately than is an automatically regulated movement. Indeed, it not infrequently happens that when a normal individual attempts to execute some difficult feat particularly well,—i.e., when he watches each individual movement—the feat is done particularly badly. This shows the superiority of the automatic regulation over the volitional. A compensation for losses of centripetal control may be developed, however, in another way.

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[29] Strümpell, Ztft. f. Nervenheilk., vol. xxiii. p. 1.

[30] Lüthje, Ztft. f. Nervenheilk., vol. xxii. p. 280.

When the sensory impulses from the affected extremity are not all shut off, then the patient may learn to utilize those that are left to a far greater extent than they were ever used previously, and so to develop a new automatic regulation.

Disturbances of sensation may affect the functions of the body in other ways than by causing ataxia;[31] and here again the loss of certain sensations may be compensated for, to a certain extent, by other sensations, and especially by those that come from the eyes. For this reason,,it frequently happens that such disturbances only become manifest when the patient closes his eyes. When the sense of touch in the hands is lost, the patient is unable to grasp objects properly or to gain an idea of the contour of surfaces, unless the eyes follow the movements of the hand. If the senses of position and of motion are diminished, then all the finer movements that depend upon the position of the body or of the hand in space are not executed accurately except under ocular supervision. The deaf-mute, whose semicircular canals are destroyed, becomes unsteady so soon as his eyes are closed, just as does the ataxic tabetic, etc.

The Effect upon Motion of Variations in the Reflexes.— Although the reflexes have been carefully studied, especially in regard to their diagnostic significance, very little attention has been paid to the important influence that they exert upon our voluntary movements, owing to the effect that they have upon the state of contraction of the muscles. In addition to this they serve to protect the joints from forcible and sudden motions. [32]

It is extremely difficult to estimate the precise injury that is caused by an absence of the tendon reflexes, for such absence is usually associated either with paralysis or with definite

[31] Exner, Pflüger's Arch., vol. xlviii. p. 592; Strümpell, Ztft. f. Nervenh., vol. xxiii. p. 1.

[32] Sternberg, Die Sehnenreflex, Leipzig, 1893, p. 272.

sensory changes. When the reflexes are much exaggerated, the tension of the muscles is increased to such a degree that the slightest irritation will call forth a reflex spasm. With every motion, the tendons and ligaments, especially those opposing the movement, are put more or less on the stretch. This initiates reflex muscular contractions, which tend especially to affect the antagonists of the muscles that are innervated. As a result, all movements become stiff, and in very bad cases even impossible. This reflex innervation of antagonistic muscles may cause such uncertainty of movement that the resulting picture resembles true ataxia.[33]

Nervous Disturbances of Urination and Defecation.— The reflex acts of urination and defecation are so far under the control of the will that, up to a certain limit, we can inhibit or initiate their taking place. The nervous impulses running from the brain to the lower centres merely prevent or permit the peripheral sensory impulses from initiating the reflex act.

The reflex centres that control defecation and urination are not situated in the cord, as has been generally supposed. They lie in the sympathetic system.[34] The centripetal impulses that these centres receive from their corresponding organs are, in part, excited by distention of the organ. Yet distention is only one of the factors that initiate the reflex, for we urinate different amounts at different times, and much less when the mucous membrane of the bladder is inflamed or when the urine is concentrated, highly acid, and irritating.

In the new-born infant, urination and defecation are purely reflex phenomena. When the centripetal impulses become sufficiently strong, the reflex mechanism is set in action and the viscus is emptied. Only through careful training does the child learn to govern these reflexes and gradually to bring them within the normal limits of control.

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[33] H. E. Hering, Prag. med. Wochens., 1896.
[34] L. R. Müller, Ztft. f. Nervenheilk., vol. xxi. p. 86.

If the impulses running from the cerebrum to the lower centres be interrupted from any cause, then voluntary control over evacuation is lost. For a time after these impulses are cut off, the bladder remains full and continually overflows (incontinence from retention), but gradually it comes to empty itself reflexly at intervals, just as it does during infancy. Since this reflex emptying of the bladder may occur even when the lumbar cord is destroyed, the centre lies outside the cord.[85]

Other nervous lesions cause various other disturbances. For example, a loss of centripetal impulses from the bladder to the reflex centre will lead to a pure retention, and a diminution in these impulses will lead to difficulty in passing urine, to straining, and to delay in starting the stream. Lesions of the motor paths may cause similar disturbances, such as slow urination and the retention of urine in consequence of a paresis of the detrusor, and continual dribbling in consequence of a weakness of the sphincter. Irritative lesions of the tracts that connect the cerebrum with the reflex centre may cause retention of urine from spasm of the sphincters. Finally, it must be remembered that the external sphincter is a voluntary muscle, and that when it is paralyzed there may result merely an inability to hold the urine when the bladder becomes filled.

The nervous disturbances of defecation appear to be very similar to those of urination.

Pathological Alterations in the Reflexes.—In a pure reflex, the sensory impulse acts immediately upon the motor apparatus without the intervention of the will. The reflex mechanism consists, therefore, of the sensory apparatus, the motor apparatus, and the connection between the two. The latter may be situated either in the brain, the spinal cord, or the sympathetic system.

(*a*) *The Deep Reflexes.*—Those reflexes which arise from

[85] L. R. Müller, loc. cit.

the tendons, periosteum, or bones, and of which the patellar reflex is the best-known example, traverse the spinal cord or the subcortical portions of the brain. They are subject to many and different influences, which latter may act either directly upon the sensory or motor apparatus or, more indirectly, may tend to inhibit or to further the transference of the impulse from the sensory to the motor side of the reflex arc.[36]

Even normally there is a great variation in the intensity of the reflexes, not only in different individuals, but in the same individual at different times, the latter being especially true of " nervous" patients. The reflexes tend to be exaggerated during fatigue, as well as in marantic and cachectic conditions. They show considerable variations in the infectious diseases. They usually disappear just before death.

If the reflex arc be broken at any point, whether in the sensory, the motor, or central portion, then the corresponding reflex is abolished. In the earliest stages of tabes dorsalis, for example, the knee-jerks may be absent because that part of the cord has degenerated through which the sensory portion of the reflex must travel. Even when the reflex is absent, however, it is possible that the path is not completely blocked, but only sufficiently so to inhibit the reflex taking place under ordinary conditions. If such be the case, then a cerebral lesion that would normally increase the reflex may cause the lost one to return. This has been observed in a number of cases.[37]

A disease of the reflex arc, such as a neuritis, at times causes an exaggeration of the corresponding reflex.[38] It is

[36] Sternberg, Die Sehnenreflex, 1893; Jendrassik, Arch. f. klin. Med., vol. lii. p. 569; Strümpell, Ztft. f. Nervenheilk., vol. xv. p. 254; Kornilow, ibid., vol. xxiii. p. 216.

[37] See Sternberg, loc. cit., p. 178.

[38] Strümpell and Möbius, Münch. med. Wochens., 1886, No. 34; Sternberg, loc. cit.

possible that, in these cases, the inflamed sensory nerves show an increased irritability or conductivity; though it is also possible, as Sternberg believes, that the exaggeration is caused by changes in the reflex centre.

The deep reflexes may be influenced by lesions that lie outside of the reflex apparatus itself. The most important of these are the lesions which interrupt the passage of impulses from the cerebrum, or possibly also from the subcortical centres, down to the lower spinal reflex centres. Injuries of this character are usually followed by an exaggeration of the deep reflexes, and it has been assumed that this results from a blocking of the inhibitory influence which the brain is supposed to exert upon the spinal centres.[39] Yet the correctness of this interpretation may justly be questioned, for numerous observations have established the fact that the patellar reflexes may totally disappear after a complete transverse section of the spinal cord.[40] In some such cases, however, the tendon reflexes have persisted in spite of the transverse lesion, and experiments upon dogs and monkeys have yielded equally conflicting results. In them, a complete section of the cord may be followed either by increased or by diminished reflexes. Immediately after the operation on these animals, the reflexes are usually abolished, but they gradually return after a certain length of time. The primary injury itself may possibly inhibit them for a time, thus causing their primary disappearance; but their continued absence in clinical cases cannot be accounted for in this manner. Possibly some secondary degenerations take place in the fibres of the reflex arc, and these account for the continued absence of the reflexes.

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[39] Bickel, Ztft. f. Nervenheilk., vol. xxi. p. 304.

[40] Sternberg, loc. cit.; D. Gerhardt, Ztft. f. Nervenheilk., vol. vi. p. 127; L. Bruns, Arch. f. Psych., vol. xxv. p. 759; vol. xxviii. p. 133; Nonne, ibid., vol. xxxiii. p. 393; Kron, Ztft. f. Nervenheilk., vol. xxii. p. 24; Kausch, Grenzgeb., vol. vii. p. 541.

(*b*) *The Superficial Reflexes.*[41]—These reflexes are of a more complex character than are the deep reflexes, and their nature is less understood. A relatively slight stimulus applied to the skin or to a mucous membrane will often elicit a relatively strong response, and the resulting movements are usually slower and more under the control of the will than are the deep reflexes. It is quite possible that the nervous path that some of these skin reflexes follow traverses the cerebrum, and that this is the reason why they are so often absent in the very conditions in which the tendon reflexes are exaggerated. Yet this is very questionable, and the data at our disposal do not permit us even to formulate any exact hypothesis as to the nature of the superficial reflexes.

Strychnine Poisoning and Tetanus.—The violent muscular contractions that characterize these conditions are caused by an increased irritability of the cells in the spinal cord.[42] In strychnine poisoning, the convulsions are of a purely reflex character; *i.e.*, they are excited by sensory impulses from the periphery. In tetanus some are of this character, whereas others are due to a primary stimulation of the large motor cells in the cord. These cells certainly become abnormally irritable in tetanus, and some remarkable anatomical changes in them have been described.[43]

The brilliant researches of Meyer and Ransom [44] have shown that the tetanus toxin travels from the periphery to the

[41] See Jendrassik, Arch. f. klin. Med., vol. lii p. 569; Strümpell, Ztft. f. Nervenheilk., vol. xv. p. 254.

[42] Brunner, Beitr z. klin. Chir., vol ix. pp. 83, 269; vol. x. p. 305; vol. xii. p. 523; Deut. med. Wochens, 1894, No. 5; Gumprecht, Deut. med. Wochens., 1895, No. 42; Courmont and Duyon, Arch. de Physiol., vol. xxv. p. 64; Goldscheider, Ztft. f. klin. Med, vol. xxvi. p 175.

[43] Goldscheider and Flatau, Fortschritte, etc., 1897, p. 609; 1898, No. 6; Westphal, ibid., No. 13.

[44] H. Meyer, Sitzungsber. d Gesell z. Beför. d. Naturw. in Marburg, 1902, No. 1; Meyer and Ransom, Arch. u. exp. Path, vol. xlix. p. 369.

spinal cord through the axis cylinders of the nerves, and that it cannot attack the cord directly from the blood or lymph. The nerves must first be entered. For example, if the tetanus anti-toxin be injected into certain nerve-trunks of an animal, and if at the same time the toxin be injected into the blood or lymph, then the regions corresponding to the nerves that have received the antitoxin are not affected during the ensuing tetanus. When tetanus toxin is injected directly into the spinal cord, the incubation period ·that elapses before the appearance of symptoms is reduced to about two and a half hours. This demonstrates that the long incubation period, usually present in tetanus, is due to the time consumed by the toxin in travel-ling from the periphery to the central structures.

The tetanus toxin first affects the motor cells of the cord in such a way as to irritate them and to cause a tonic spasm of the corresponding muscles, which spasm is not of a reflex char-acter. The toxin then spreads to neighboring cells, especially to the motor cells lying on the opposite side of the cord, with resulting convulsions in the same muscles as those first af-fected, but on the opposite side of the body. Still later, the poison affects the sensory portion of the reflex arc, and we then get reflex convulsions; yet only · those reflexes are in-creased which pass through the affected parts of the cord.

The sensory nerve-fibres do not seem to be affected by the tetanus toxin under ordinary conditions; yet Mayer and Ran-som have shown that if the toxin be injected directly into the posterior nerve-roots, the first symptoms of the poisoning are attacks of violent pains, the so-called tetanus dolorosus.

Tetanus in man differs from that produced experimentally in animals, inasmuch as the muscles first affected are usually those of the jaw, producing the well-known trismus; whereas experimentally the convulsions begin in the muscles that corre-spond to the point of inoculation.

Contractures.—The bones about a joint are not infre-

quently held in a more or less fixed position. This may be due to a number of causes, such as diseases of the joints, scars in the skin or muscles, and changes in the muscles, either primary or secondary to nervous lesions. Any of these might be termed contractures, but it is customary to limit the use of the term to those limitations of motion that follow diseases of the muscles or of the nerves.

(*a*) *Passive Contractures.*—If, for any reason, certain muscles remain shortened over a long period of time, this shortening tends to become permanent, and the movements of the joint are then correspondingly limited. This condition is spoken of as a passive contracture. Of the causes that may lead to such a shortening of the muscles, we may name the maintenance of a certain posture for a long time. In this manner, a drop-foot is not infrequently produced by the pressure of the bedclothes during a long illness. When certain groups of muscles are weakened or paralyzed, either from disease of the muscles themselves or from disease of their nervous connections, then the antagonistic muscles, not meeting with the normal resistance to their action, tend to move the joint into an abnormal position and to hold it there. Whenever the joint has been held in a certain position for a long time, it tends to be fixed in this position both by the development of adhesions about the joint itself and by anatomical alterations in the shortened muscles. Passive contractions have been produced experimentally in monkeys by the extirpation of portions of the cerebral cortex, and by subsequently keeping the animals in such small cages that their movements are very much limited.[45]

(*b*) *Active Contractures.*—In active contractures, the joints are held in an abnormal position by the tonic contraction of certain groups of muscles. Since there is usually an associated increase in the tendon reflexes in these cases, they have

[45] H. Munk, Du Bois' Arch., 1896, p. 564.

been termed by some, spastic contractures. The cause of the muscular spasm which produces the contracture is not always clear, and it may not be the same in all cases. As we have said, the reflexes are usually exaggerated in active contractures, yet not necessarily so, and in some cases they remain unaffected.

When the reflexes are increased, the contractures might possibly be caused by a reflex stimulation of certain groups of muscles about the joint. To my mind, however, this explanation is not a very satisfactory one, and it seems very probable that, in many cases, at least, the contractures and the exaggerated reflexes are both due to a common cause.

Mann has given a very plausible explanation of post-hemiplegic contractures.[46] He first calls attention to the fact that these contractures affect especially the muscles that are least paralyzed. In the complicated innervation that directs every voluntary movement, there is apparently not only a stimulation of the muscles that produce the movement, but an inhibition of the antagonistic muscles. A cerebral disease, therefore, will not only paralyze certain muscles, but it will at the same time diminish the inhibitory impulses sent to their antagonists. This lack of inhibition would explain the contracture in the antagonistic muscles, and Mann's hypothesis accords very well with the experimental results of H. E. Hering.[47] In many instances, irritative processes seem to cause the tonic muscular spasm, though it must be admitted that no very sharp line can be drawn between an irritation and a diminution of inhibitory influences.

(c) *Contractures from Joint Disease.*—Two views have been advanced as to the cause of the contractures that develop in joint diseases. According to the one, the muscle spasm is

[46] Mann, Monatschr. f. Psych. u. Neurol., vol. i. p. 409; vol. iv. pp. 45, 123.

[47] Pflüger's Arch., vol. lxx.

caused reflexly from the joint, owing to a strong stimulation of the sensory nerves there. This view is supported by the fact that the tendon reflexes are often increased in these conditions. Personally, however, I am inclined to favor the view that the muscle spasm and peculiar posture assumed by these patients are both the result of a desire to avoid pain; though it must be admitted that this does not explain the increased tendon reflexes.

(d) *Hysterical Contractures.*—Hysterical contractures are usually, but not always, associated with exaggerated reflexes. They would appear to be due in part to this exaggeration; in part, perhaps, to a diminution of the inhibitory control normally exercised by the brain over the lower spinal centres.

Motor Irritative Symptoms. (a) *Tremor.*—Tremor may be defined as a series of regular oscillatory muscular movements about a fixed axis. The rate of these oscillations, their amplitude, and the number of muscles affected, all vary in individual cases. In many conditions the tremor only occurs during voluntary movements; in others, it is more intense during rest. All forms of tremor cease during sleep. Unfortunately we cannot discuss tremor, because, in our opinion, absolutely nothing is known as to its real cause,[48] and because it is not our purpose to enter into clinical or diagnostic details.

(b) *Choreiform Movements.*—According to Bonhoeffer, the choreiform movements that sometimes develop after a hemiplegia are usually caused by lesions of the superior cerebellar peduncles,[49] which lesions would interrupt the centripetal impulses that pass through the cerebellum on their way to the motor region of the cerebral cortex. The muscle tonus in these conditions is usually diminished,[50] which fact lends

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[48] See Möbius, Diagnostik, second edition; Stephan, Arch. f. Psych., vol. xviii. p. 734; vol. xix. p. 18.

[49] Monatshefte f. Psych. u. Neuro., vol. i. p. 6; vol. x. p. 383.

[50] Bonhoeffer, Monatshefte f. Psych. u. Neur., vol. iii. p. 239.

some support to this hypothesis that the cerebellar function is affected.

(c) *Associated Movements.*—In a variety of pathological conditions, certain voluntary movements are regularly accompanied by other purposeless, so-called associated movements.[51] As we have already stated, the innervation for a voluntary movement is extremely complex, impulses being sent to a great number of muscles. The muscular contractions that would result from all these motor impulses are, however, controlled by other impulses that come in from the periphery. If this peripheral control be lost, it is possible that certain acts should be accompanied by extra, purposeless movements which would be suppressed in the normal individual. The associated movements that may occur in tabes dorsalis are therefore related in a way to the ataxia, for both depend upon a loss of centripetal, peripheral control.

(d) *Convulsions.*—Convulsions may be of the clonic type, —i.e., the muscles are alternately contracted and relaxed with corresponding movements of different parts of the body; or they may be of the tonic type,—i.e., the contraction is continuous and the parts affected simply become rigid. Finally, the two forms of convulsions, tonic and clonic, may alternate with each other.

Convulsions are undoubtedly caused by a stimulation of the motor tracts or nerve-cells. A disease of the cervical or dorsal cord may cause convulsive movements in the legs from an irritation of the motor tracts; lesions of the internal capsule or of the cerebral cortex may cause convulsions in the corresponding extremities, etc. It would appear, however, that the stimulation of the cerebral cortex is more liable to produce convulsions than is stimulation of other parts of the motor apparatus.

[51] See Foerster, Die Mitbewegungen, Jena, 1903.

Many poisons produce convulsions, some of which, such as the uræmic poison, are formed within the body during pathological processes. It is impossible to say, however, upon which part of the central nervous system these poisons act.

Epilepsy is apparently due to an excessive irritability of the central nervous structures. The convulsions themselves may be precipitated by sensory impulses from some part of the surface of the body, but more frequently they come on spontaneously, or, at least, without any discoverable cause. The attack is often preceded by certain characteristic psychic or bodily warnings (aura). The patient then becomes unconscious and general convulsions occur, which are at first tonic but later clonic in character.[52] It is possible to induce tonic as well as clonic convulsions in animals experimentally by stimulating various parts of the brain, such as the medulla, the pons, and the sensory and motor regions of the cortex. Of these convulsions, none present so great a similarity to the attacks of epilepsy as do those that follow stimulation of the cerebral cortex. The latter may be either fully developed or rudimentary in type, and they often continue after the stimulation has ceased. The similarity that exists between the convulsions of epilepsy and those that follow stimulation of the cerebral cortex favor the view that epilepsy is of cortical origin. This view is supported, furthermore, by certain clinical facts, such as the frequency of rudimentary epileptic attacks, the associated unconsciousness, the spread of the convulsions in accordance with the cortical representation of muscles, and the frequent occurrence of sensory aura.

Disturbances of Sensation.—The pathology of sensation is so intimately associated with the mind itself that our consideration of this subject will necessarily be limited, for, as we have already said, we do not propose to discuss psychic

[52] See v. Biswanger, in Nothnagel System.

changes. It will be necessary to limit our discussion in still another way,—viz., by omitting the special senses of sight and hearing, for these subjects require so much special knowledge that we cannot do justice to them.

Disturbances of sensation may be either irritative or paralytic in character, and the sensory mechanism may be injured at any point from its beginning in an end organ at the periphery to its termination in the central perceptive part of the cerebrum. If the peripheral sense organ is injured, if conduction of the impulse through the nerve or cord be interrupted, or if, finally, the connections in the brain be thrown out of function, then the sensation will be either distorted in some manner or it will not be perceived at all.

In certain spinal or peripheral diseases the sensations are, indeed, perceived, but they travel at a slower rate of speed than normal. This occurs most frequently in tabes dorsalis and it most frequently affects the cutaneous sensation of pain. We do not know exactly how this delayed sensation is caused.

When a certain injurious agent affects at one time a number of nerve-fibres of different functions, then the sensory fibres usually resist the injury better than the motor fibres do. Under such circumstances, the motor fibres may be paralyzed, while the sensory fibres are merely irritated and cause pain. This combination of symptoms is seen especially from pressure upon the spinal cord, in which case we have the characteristic picture of paraplegia dolorosa.

Our whole knowledge of the external world comes to us through centripetal nervous impulses, all the functions of our bodies being more or less affected by them. Thus, the sensations of light, sound, and temperature influence metabolism, muscular activity, and respiration. When one form of sensation is lost, the others become more acute because more attention is directed to them, the best known example of this being the acute sense of touch that is developed in blind individuals.

The Cutaneous Sensations.—The nerves of pressure, pain, heat, and cold, each possess definite and characteristic endings in the skin.[53] These delicately constructed end organs are almost certainly injured in some skin diseases, although, so far as I know, no thorough study of such injuries has yet been made. Diseases of the nerves or of the central apparatus may also affect the cutaneous sensations, and any one of the latter may be disturbed without the others being affected. Such "partial anæsthesias" may result from disease either of the nerves or of the central nervous system, but they are especially frequent in tabes and in syringomyelia. The occurrence of such partial anæsthesias is of great practical and theoretical interest, for it implies that special nerves exist for each of the cutaneous sensations. In particular, it tends to prove that pain is due to the stimulation of special pain fibres, and not to the overstimulation of other varieties of fibres. The physiological observation that certain points in the skin are sensitive to pain alone and others to pressure alone, likewise supports this view. We may mention, however, that even so experienced an investigator as Goldscheider denies the existence of special nerves for pain.[54]

Lesions of the peripheral nerves may affect the different skin sensations to different degrees, and in this manner give rise to partial anæsthesias; but the most pronounced instances of this condition are usually observed in diseases of the spinal cord. The fibres that transmit the various forms of cutaneous sensation apparently run in different parts of the cord, and, consequently, a limited lesion may block some of them and leave others intact.

The path pursued by the sensory fibres in the central nervous system is an extremely complex one. A portion of the

[53] See v. Frey, Berichte d. Kgl. S. Ges. d. Wissenssch., math-phys. Kl., March, 1895.

[54] Goldscheider, Ueber den Schmertz, Berlin, 1894.

fibres that carry impulses to the brain certainly cross by way of the anterior commissure to the opposite side of the cord shortly after they enter it.   This is the explanation of the Brown-Sequard symptom-complex.   If one-half of the spinal cord be destroyed, the muscles on that side below the level of the lesion will be paralyzed, with an associated loss of the sense of position.   The cutaneous sensations, that are interrupted, however, are those that come from the opposite side of the body below the lesion.

When the sensory tracts reach the brain, they connect with various reflex and automatic centres, and some finally terminate in the cerebral cortex, apparently in the neighborhood of the motor areas that govern the movements of corresponding parts of the body. For this reason, lesions of the cortical motor area usually produce a diminution, though not a complete loss, of sensation in those parts of the body that correspond to the paralysis.   So far as sight and hearing are concerned, we know that a sensation may be perceived without its meaning being recognized (soul blindness).   For example, a patient may hear the ringing of a bell but yet be unable to tell what causes the sound.

Every sensation produces at the same time a more or less definite impression of the place whence the sensation has come. In the case of the eyes and skin, this localization is very accurate, in the case of the mucous membranes near the outside of the body it is somewhat less accurate, and in the case of the deeper mucous membranes and the organs within the body, it is inaccurate and entirely unreliable.   In certain nervous lesions, especially in those about the optic thalami,[55] the cutaneous sensations are perceived but the ability to localize them is more or less lost.   The exact nature of the changes that cause this loss of localization are not well understood.

⁵⁵ Horsley, Practitioner, 1904.

The Orientation of our Bodies in Space.[56]—We derive information as to the position of our bodies in space from a number of sources. Our eyes aid us by means of the images upon the retinæ and by their motion within the orbits, the internal ear enables us to estimate changes in the rate or direction of our movements, and other more or less valuable data are derived from the muscles, tendons, bones, joints, skin, etc. Even though we are not conscious of these various sensations, they all influence to some extent the conception that we have as to our position in space.

Certain of these sensations may be lost without much effect upon our powers of orientation, for the reason that other sensations compensate for the lost ones.[57] The blind man moves about a room with great precision so long as he can use his sense of touch, and the deaf-mute hardly seems to be affected by the loss of his internal ears. It is an interesting fact, however, that deaf-mutes do show a diminished power of orientation, and that they behave quite differently from normal individuals when they are turned about rapidly.[58] The tabetic who has lost certain of the sensory impulses coming from his legs depends very much upon his visual impressions, and if these be taken away from him by closing his eyes, he will often immediately fall to the ground. We see, therefore, that various disturbances of the peripheral sensory apparatus will disturb the sense of our position in space. The same effect may also result from lesions of the central mechanism in the brain; above all, from lesions of the cerebellum.

Dizziness.—We do not mean by dizziness a partial, transitory loss of consciousness, but a feeling that we are unable to control our equilibrium. This feeling usually results from an inability on the part of the central apparatus to harmonize the

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[56] See Hartmann, Die Orientierung, Leipzig, 1902.

[57] See Bickel, Deut. med. Wochens., 1901, No. 12.

[58] Kreidl, Pflüger's Arch., vol. li. p. 119.

various centripetal impulses that come to it.[59] For example, if certain ocular muscles are paralyzed, then the images of an object looked at do not fall upon corresponding points of the two retinæ as they normally should, and consequently the impressions derived from the two eyes will not correspond to each other. This causes a sensation of dizziness, which may usually be relieved if the impressions derived from the offending eye are excluded by closing it. Diseases of the semicircular canals, of the sacculus or utriculus, or of their central nervous connections in the cerebellum, will likewise cause dizziness, which dizziness is most marked when the disease is limited to one side only.

In aural vertigo (Ménière's disease) the dizziness is usually associated with disturbances of hearing. The cochlear branch of the auditory nerve transmits sensations of sound; whereas the vestibular branch, proceeding from the vestibule and the semicircular canals, carries impulses that are caused by changes in the rate or direction of our movements. The symptom of dizziness in aural vertigo undoubtedly results from disturbances in the impulses carried by the vestibular nerve. The associated anomalies of hearing are easily understood when we consider the close proximity of the two nerves and of their end organs. In many cases the sensations of dizziness will disappear if the patient remain perfectly quiet; whereas in other cases they are constantly present even though the patient be still, and under such circumstances they are most harassing.

The dizziness of aural vertigo is probably due to an irritation of the vestibular nerve or of its connections rather than to a mere lack of function. The patient becomes dizzy because the impressions received from this source do not coincide with those received from other parts of the body. That the dizzi-

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[59] See Hitzig, in the Nothnagel System.

ness in these cases is not due to a mere lack of sensation from the internal ear is rendered probable by the fact that the typical symptoms of aural vertigo are rarely seen in those deaf-mutes in whom the internal ear is entirely functionless.

Aural vertigo, as well as cerebellar vertigo, is frequently associated with other symptoms, such as vomiting, uncertainty in the voluntary muscular movements, especially in walking, and peculiar movements of the eyes. At present, however, it is impossible to explain these associated symptoms very satisfactorily.

The sensation of dizziness may also be produced by many other causes, such as alcoholic intoxication, cerebral pressure, anæmia, and circulatory disturbances; yet the exact mode of its causation in these conditions is not known.

Hyperalgesia.—Increased sensitiveness to painful stimuli that are applied to the skin has been observed in various diseases of the cord and of the more central endings of the sensory tracts. The transition from the normal to the pathological, however, is here a very gradual one, and individuals of a " sensitive" nature are certainly more susceptible to pain than are those of a phlegmatic type. The hypersensitiveness of hysterical patients is probably of this perceptive character. Peripheral abnormalities rarely give rise to hyperalgesia, although a neuritis will sometimes do so.

Irritative Sensory Symptoms.—These differ from the preceding in that the pain results not from hypersensitiveness to normal stimuli, but from a pathological irritation of the sensory mechanism.

Itching is apparently caused in all cases by an irritation of the sensory organs in the skin, and it never results, so far as I am aware, from lesions of the conducting apparatus. It accompanies most cutaneous diseases, but, for some unknown reason, it tends to be absent in certain lesions, such as those produced by syphilis. Not infrequently, itching is present

when no cutaneous changes can be demonstrated, as, for example, in jaundice and diabetes. It is possible that in these cases the central apparatus is directly irritated. On the other hand, paræsthesias, such as numbness and tickling, rarely accompany cutaneous diseases, but are caused usually by nerve or cord lesions. They have also been observed in the extremity that corresponded to a point of softening in the sensory sphere of the cerebral cortex.[60] They seem, therefore, to be caused by an irritation of the sensory tracts.

Abnormal sensations of heat and cold are sometimes experienced, but it is often difficult to distinguish these from the accompanying sense of pain.

In our opinion, pain is normally caused by the stimulation of special pain fibres or sensory end organs. Heavy pressure, for example, will deform the skin and so stimulate the pain points. Pain also results from various inflammations and degenerations of the nerves, such as may be caused by alcohol, arsenic, malaria, etc. The nerves may also cause pain even when no demonstrable lesion is present, as happens in the neuralgias.

It is remarkable that pathological processes within the central nervous system itself rarely produce much pain, so long as the peripheral nerves, the posterior roots, and the meninges remain unaffected. Surgeons and physiologists have frequently demonstrated that the brain itself is practically insensible; and although it cannot be denied that the pain fibres may be stimulated within the central nervous system,[61] yet the general fact remains that such a stimulation is not easily brought about.

Many hysterical pains are probably of a central, " psychic" nature, but these are not related in any way to organic lesions of the cerebral cortex.

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[60] Ziehen, Ergebnisse, etc., p. 604.

[61] Edinger, Ztft. f. Nervenheilk., vol. i. p. 262; Reichenberg, ibid., vol. xi. p. 349; Goldscheider, Ueber den Schmertz, Berlin, 1894, p. 24, etc.

The Influence of the Nervous System upon the Tissue Nutrition.—The nutrition of a tissue depends primarily upon the activities of its individual cells. It is, indeed, necessary that food material should be supplied to it from the blood in sufficient quantities, yet this food supply alone does not stimulate the growth of the cell. That stimulus must come from the parenchyma itself.

The exact part that the nervous system plays in this process is not at all clear. Beyond question, it exerts a very important influence upon the nutrition of certain tissues. Is this influence, however, due merely to the fact that the cells do not functionate properly without nervous impulses, or do the nerves contain some specific, nutritional, " trophic" fibres?

The Effect of Separating a Nerve-Fibre from its Cell.— The nerve-fibres degenerate if they are separated from their ganglion cells, or if these cells are destroyed. This is explained, according to the neuron theory, on the assumption that the nerve-fibre, a long process of the ganglionic cell, dies when it is separated from its mother cell. Some, indeed, claim that the mere separation of the fibre from the cell, or, rather, the cessation of the influence that the cell exerts over the fibre, is not the cause of the degeneration, but that the latter is due directly to the traumatism of the operation.[62] It is possible, for example, experimentally to interrupt the transmission of nervous impulses through a fibre for a very long time without having any degeneration take place; but although the ordinary nervous impulses were interrupted in such a case, we cannot be sure that the nutritional impulses were likewise affected.

Even though the nerve-fibre is a part of the ganglion cell, the two must be, to a certain extent, independent of each other, for the fibres seem to be relatively much more susceptible to the action of certain toxins. The neuritis that follows the circula-

[62] Bethe, Allgem. Anat. u. Path. d. Nervensyst., Leipzig, 1903.

tion of these toxins in the blood apparently occurs either be-
cause these fibres contain elements for which the toxins show a
special affinity, or because the fibres are so remote from their
nutritional centres, the cells. In many cases the nerves are ca-
pable of exchanging material with their surroundings, as is
evidenced especially by the fact that the tetanus toxin travels
from the periphery to the cord through the axis cylinders.
Possibly the toxins of other infectious diseases pursue this
same course, and, if this were so, it might explain the special
susceptibility of the nerve-fibres to the toxins of infectious
processes.

In some instances, as in a lead poisoning, different portions
of the nerve-cell may be affected and consequently widely dif-
ferent nervous symptoms may be produced. Certain of the sys-
temic diseases of the spinal cord show various transitions into
each other, and it is easy to conceive, for example, that the
same cause might produce in one person a progressive muscular
atrophy, in another, an amyotrophic lateral sclerosis, and in a
third, a true spastic paraplegia, depending upon whether the
pyramidal tracts or the motor cells of the anterior horns were
more especially affected.

When a ganglion cell is separated from its peripheral
neuron, the former also undergoes certain changes,[68] which
reach their height in about eighteen days. After this a portion
of the injured cells may be restored to their normal condition.
If the cell continue to be functionless, however, for the reason
that the peripheral nerve cannot regenerate, then it gradually
undergoes atrophy. This happens, for example, after amputa-
tions, and the younger the individual the greater is the cell
destruction. These facts are of considerable theoretical inter-
est, for they show that the normal existence of a ganglion cell
depends largely upon its ability to exercise its function. De-

[68] Marinesco, Neurol. Zrtbl., 1892, pp. 463, 505, 564; Nissl, Ztft. f.
Psych., vol. xlviii. p. 197; Bethe, loc. cit.

generation occurs because the sensory cells receive no impulses from the periphery and because the motor cells no longer receive those indirect stimuli from the muscles and other tissues which normally play so great a part in the regulation of their activities.

Nutritional Disturbances in the Muscles.—When the muscles are separated from the spinal cells that innervate them, they degenerate. The degenerative changes consist mainly in alterations of their chemical composition [64] and of their electrical irritability. In addition to these, a simple reduction of their contractile substance without degenerative changes takes place.[65] The reduction of the quantity of protoplasm is caused by the inactivity, and it is, therefore, an atrophy from disuse. The microscopical signs of degeneration, such as the granular and waxy degenerations, are not due to the separation of the muscles from the cord, but to some associated action of toxic substances.

Changes in the Electrical Irritability of Muscles.[66]—After a muscle has been separated from its ganglion cells for a certain time, it responds abnormally to the electric current, and these changes constitute the so-called reaction of degeneration. It will no longer contract when its nerve is stimulated in any manner by the electric current, nor will it contract when it is itself directly stimulated by an ordinary interrupted current. Even the healthy muscle does not contract if very high frequency currents are applied to it, so that the loss of irritability, that the degenerated muscle shows toward an interrupted current, is merely one of degree. It is an exaggeration of the normal. In this respect, the degenerated muscle behaves like

[64] Rumpf and Schum, Ztft. f. Nervenheilk., vol. xx. p. 445; Rumpf, Arch. f. klin. Med , vol. lxxix. p. 158.

[65] See Jamin, Exp. Untersuch. z. Lehre v. d. Atrophie gelahmter Muskeln, Jena, 1904.

[66] See Erb, Electrotherapie, second edition; Stintzing, in Penzoldt-Stintzing's Handbuch d. spec. Therapie.

a smooth muscle, for the latter also usually fails to respond to an interrupted current.

The muscle that is separated from its ganglion cells will, however, respond for a long time to interruptions of the galvanic current, and it will, indeed, respond to a much weaker current than does the normal muscle. The contraction produced by this current is not a prompt and short one, as is the case with the normal muscle, but it is very slow, and easily passes into tetanus. Such a slow contraction is also seen in the smooth muscle, in the fatigued striated muscle, and in myotonia congenita. Yet in all of these conditions the muscular contractions differ in other respects from that of the degenerated striated muscle.

The degenerated muscle, instead of responding more strongly to a closure of the current when the cathode is placed upon it, frequently contracts more strongly to the anodal closure. It has been commonly assumed that this change is due to some fundamental alteration in its protoplasm, whereby it is rendered more irritable to the anodal closure; yet such does not seem to be the case. The muscle conducts the current, and, when the cathode is placed over its centre, for example, the current enters at the end and this receives an anodal stimulation. In the normal muscle the cathode causes a stronger contraction, because it is placed over the point of greatest irritability; i.e., the entrance of the nerve into the muscle. The centre of the degenerated muscle, however, early loses its irritability, and the extremities become the most irritable parts. When, therefore, an electric pole is placed over the centre of a degenerated muscle, and the current is closed, the end of the muscle receives the main stimulation. For this reason the maximal contraction is obtained when the anode is placed on the muscle, for the cathodal stimulus then acts upon the more irritable extremity of the muscle.[67] If the degenerated sar-

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[67] See Wiener, Arch. f. klin. Med., vol. lx. p. 264.

torius muscle of a frog be isolated and stimulated, it shows no diminution in its irritability to the cathodal closure as compared to the anodal closure.[68]

In certain instances, such as in trichinosis [69] and some muscular dystrophies,[70] the reaction of degeneration has been present without demonstrable lesions of the nerves. At the present time, however, these cases cannot be accepted as proof that the reaction of degeneration may occur independently of nervous lesions, for it is almost impossible to exclude changes in the finer nerve filaments.

When a motor nerve is injured, but not entirely destroyed, then electrical changes of a less marked degree take place in the muscles,—the so-called partial reaction of degeneration.[71]

Atrophy from Cerebral Lesions.—When muscles are paralyzed from a cerebral lesion, the resulting atrophy develops more gradually and is of slighter extent than that which follows the division of a peripheral nerve, and it is, furthermore, unaccompanied by any reaction of degeneration. In such cerebral paralyses only one form of stimulation, the voluntary, is shut off from the paralyzed muscle. The reflex and automatic stimulations from the lower centres continue to act upon it. The paralyzed muscles frequently do contract from reflex stimulation, and even when they do not apparently do so, they still maintain their muscular tonus. The paralyzed muscle that retains a connection with its ganglion cells exhibits a more active metabolism than the paralyzed muscle that is separated from these cells,[72] a further proof that the former maintains a certain amount of activity.

[68] Krehl, unpublished experiments.

[69] Nonne and Hoepfner, Ztft. f. klin. Med., vol. xv. p. 455.

[70] Schultze, Ueber d. mit Hypertrophie verbund. Muskelschwund, Wiesbaden, 1886.

[71] Stintzing, Arch. f. klin. Med., vol. xli. p. 41.

[72] Zuntz, Berl. klin. Wochens., 1878, No. 10.

In certain instances, especially in the young, cortical lesions have been followed by marked changes in the lower neurons and rapid atrophy of the muscles.[73] The electrical reaction in these cases is usually qualitatively normal, although in a few the slow contraction of degeneration has been present. The upper neurons apparently exercise some influence upon the peripheral neurons, and when this is cut off in early life, the latter may degenerate.[74]

Muscular Atrophy from Diseases of the Joints.[75]—These atrophies about diseased joints often develop more rapidly and are more severe than those which are caused by cerebral lesions. As a rule, they do not affect equally all muscles about the joint, but they tend especially to injure the extensors. The severity of the muscular atrophy bears no definite relation to the intensity or variety of the joint lesion. The electrical irritability of the muscle is usually reduced, but no typical reaction of degeneration is present. This form of atrophy differs, therefore, from that caused by cerebral lesions in its intensity and the rapidity with which it develops, and from that caused by nerve-lesions in the absence of a reaction of degeneration.

Various attempts have been made to explain the causation of these muscular atrophies about diseased joints. The French, following Charcot's lead, have generally considered that the nervous impulses sent from the joint to the cord influence the motor cells there, and that a disturbance of the impulses from these cells causes the atrophy. The Germans, following Strumpell, have been more inclined to attribute these muscular atrophies to an extension of the disease by contiguity from the joint to the muscle, though it must be admitted that, experi-

[73] Quincke, Arch. f. klin. Med., vol. xlii. p. 492; Steinert, Ztft. f. Nervenheilk., vol. xxiv. p. 1.

[74] Goldscheider, Berl. klin. Wochens., 1894, p. 421; Steinert, loc. cit.

[75] See Charcot's Lectures; Charcot, Progrès méd., April 1, 1893; Strümpell, Münch. med. Wochens., 1888, No. 13.

mentally at least, no inflammation of the muscle is necessarily present,[76] and that the muscles atrophy throughout their entire length, and not merely in the neighborhood of the joint. Finally, attention has been called to the fact that the most seriously affected muscles are precisely those whose movements are most limited by the joint disease, so that the atrophy is probably caused in part, at least, by disuse.[77]

The Muscular Dystrophies.—This disease, which tends to occur in families, is characterized by a very gradual atrophy of certain muscles. It usually begins in childhood or early youth. Several types have been described, but it seems very probable that they are all but different variations of the same disease. Anatomically, we find many atrophied fibres, and, in addition to these, there are usually a number of thickened fibres, which latter may, indeed, be so numerous that the muscle as a whole appears to be hypertrophied. The adipose tissue between the muscle-fibres is sometimes so increased in amount as to produce a large, weak muscle, the so-called pseudohypertrophy. In the great majority of these cases no reaction of degeneration is present, and in the few instances in which it has been found it is extremely difficult to exclude some slight involvement of the finer nerve-filaments. Even the presence of changes in the spinal cord, such as have been described,[78] do not permit us to assume that this disease is of central origin; for, as we have seen, an atrophy of the ganglion cells may follow a primary peripheral condition, such as an amputation. In a few cases, classified among the dystrophies, some complication may have caused the cord lesion.

Nutritional Disturbances of Nervous Origin in the Bones and Joints.—After an acute anterior poliomyelitis in chil-

[76] Duplay and Cazin, Arch. gén., 1891, vol. i. p. 5

[77] Sulzer, Anat. Unters. u Muskelatro artik. Ursprungs. Festschr. f. Hagenbach-Burckhardt, Basel, 1897.

[78] Erb, Ztft. f. Nervenh., vol. i. pp. 13, 173.

dren, the bones of the paralyzed extremities frequently fail to develop to their normal size; whereas, after the cerebral infantile palsies, their growth is rarely much affected. In the former cases, the absence of the varying pressures and movements, to which the bones are normally subjected, may diminish their blood-supply and so retard their development; but it is possible, on the other hand, that this retardation is due to an absence of specific, trophic influences. In adults, nutritional changes in the bones rarely result from diseases of the peripheral motor neurons alone.

In a variety of other nervous diseases, especially in syringomyelia and tabes, as well as in certain peripheral lesions, very remarkable nutritional disturbances take place in the bones and joints.[79] The anatomical changes in the joints often resemble those of arthritis deformans, but they differ from these in certain particulars, especially in the more abundant effusion, the greater destruction of the joint, the rapid course, and the frequent absence of all pain. In a certain proportion of these cases, the lesions are undoubtedly due to an absence of the senses of temperature and pain. I have myself seen a man with syringomyelia who frequently injured himself while at work from grasping live coals, who paid no attention to his wounds on account of the absence of pain, and who eventually developed the most pronounced deformities in his bones and joints. Such observations are not infrequent.[80] In locomotor ataxia, also, injuries are frequently overlooked on account of the loss of sensation in the joints and muscles. In spite of these observations, however, the opinion of the authorities is now gradually turning toward that of Charcot, who held that the arthropathies are caused, in many instances at least, by a loss of trophic impulses from the cord. Patients have been ob-

[79] Charcot's Lectures; Weizsäcker, in Bruns Beiträge, vol. iii. p. 22; Kredel, Volkmann's Vorträge, No. 309.

[80] Karg, Langenbeck's Arch., vol. xli. p. 101.

served in whom the most severe joint destructions have followed within a few days after nervous lesions, without any demonstrable mechanical injury.[81]

In some nervous diseases the bones are abnormally thin, and they fracture from very slight causes, or even, to all appearances, spontaneously. Various cord changes have been found in such patients,[82] and in some cases a neuritis has been present. Although a number of other explanations have been offered for this abnormally brittle character of the bones, it seems probable that a lack of trophic influences is the cause in many cases.

The Influence of Nervous Diseases upon the Skin.—It is well known that those parts of the skin which are exposed to continued pressure tend in time to become reddened and swollen, and eventually to die. Such ulcerations, of which bed-sores furnish the most familiar examples, may develop under a great variety of conditions, depending mainly upon the nutrition of the cells and constancy of the pressure applied. They are seen especially in patients with nervous, infectious, or metabolic diseases, who have lain for a long time in one position. In a certain proportion of the nervous cases, for these are the ones that especially interest us, the ulceration is favored by the cutaneous anæsthesia, and by the soiling of the skin with urine and fæces, owing to a paralysis of the bladder and rectum. As evidence of the importance of these factors, we may instance the brilliant results that follow the proper care of this class of patients. While we must admit, therefore, that the anæsthesia and dirt are important factors in the causation of these ulcerations, yet, in my opinion, they are not the only causes that are present, for at times the ulcers develop very rapidly even when there is no loss of sensation and no loss of bladder or rectal control. In this last class of cases, trophic

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[81] Charcot's Lectures; Riedel, Deut. Gesellsch. f. Chir , 1883, p. 93.
[82] Oppenheim and Siemerling, Arch. f. Psych., vol xviii. pp. 98, 487.

disturbances certainly play an important rôle. To what extent such trophic disturbances and to what extent the other factors enter into the causation of the ordinary bed-sores that develop during nervous diseases can only be determined by modern observations during proper care of the patient.

Herpes Zoster.—This remarkable eruption is associated with disturbances of the peripheral nerves, usually an inflammation of the sensory ganglion itself or of the nerve.[88]

The mere loss of a sensory nerve or ganglion does not cause nutritional disturbances in the skin or mucous membranes. This has been sufficiently proved by the results of extirpation of the Gasserian ganglion for facial neuralgia.[84] After such extirpations trophic disturbances of the skin over the face or of the mucous membrane of the nose or mouth do not occur. Even the cornea and conjunctivia remain intact if protected from direct injury. The keratitis observed in animals after excision of the trigeminus is due to the dry condition of the eye.[85] Since in man the eye may be kept moist by proper precautions, no keratitis necessarily results after the nerve is severed.

[88] Head, Albutt's System of Medicine.
[84] Krause, Die Neuralgie des Trigeminus, Leipzig, 1896.
[85] E. v. Hippel, Graefe's Arch., vol. xxxv. p. 217.

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